

**PERCUTANEOUS MITRAL VALVE REPAIR WITH
THE MITRACLIP CLIP DELIVERY SYSTEM
IN HIGH SURGICAL RISK PATIENTS**

**BRIEFING DOCUMENT FOR THE CIRCULATORY
SYSTEMS DEVICE PANEL ADVISORY COMMITTEE**

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List of Terms and Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ACCESS EU	Prospective, observational, multicenter, MitraClip post-approval study in Europe
AE	Adverse Event
APS	Acute Procedural Success
ASA	American Society of Anesthesiologists
ASD	Atrial Septal Defect
ASE	American Society of Echocardiography
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
BSA	Body Surface Area
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CC	Concurrent Control
CDS	Clip Delivery System
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
CI	Cardiac Index
CK	Creatine Kinase
CK-MB	Creatine Kinase-Myoglobin B
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DMR	Degenerative Mitral Regurgitation
DSMB	Data Safety Monitoring Board
Duke Analysis	Propensity Matched Analysis of MitraClip patients with Duke patients with similar demographic high surgical risk treated with medical management
Duke Cohort	953 Duke high surgical risk patients treated with medical management used for comparison to MitraClip High Surgical Risk patients in the Duke Analysis
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECL	Echocardiography Core Laboratory
EF	Ejection Fraction
ESC	European Society of Cardiology
EVEREST I	Feasibility Study of the MitraClip System (n=55)
EVEREST II RCT	Randomized Controlled Trial of MitraClip (n=184) versus Surgery (n=95)
EVEREST II HRR	High Risk Registry Arm of the EVEREST II Study; MitraClip only (n=78)
FMR	Functional Mitral Regurgitation
FSV	Forward Stroke Volume
GI	Gastro-Intestinal
HCRI	Harvard Clinical Research Institute
Integrated HSR Cohort	Integrated High Surgical Risk Cohort (n=351): EVEREST II HRR (n=78) + REALISM HR Continued Access (n=273)
HIPAA	Health Insurance Portability and Accountability Act
HR	High Surgical Risk
IABP	Intra-Aortic Balloon Pump
ICU/CCU/PACU	Intensive Care Unit/Critical Care Unit/Post-Anesthesia Care Unit
IRB	Institutional Review Board
ITT	Intention to Treat

LCB	Lower Confidence Bound
LV	Left Ventricle (or Left Ventricular)
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LVIDd	Left Ventricular Internal Diameter, Diastole
LVIDs	Left Ventricular Internal Diameter, Systole
MACCE	Major Adverse Coronary and Cerebrovascular Event
MAE	Major Adverse Event
MCS	Mental Component Summary
MI	Myocardial Infarction
MitraClip PSA Cohort	211 MitraClip High Surgical Risk patients used for comparison to Duke high surgical risk patients treated with medical management in the Duke Analysis
Modified ITT	Modified Intention to Treat
MR	Mitral Regurgitation
MV	Mitral Valve
MVA	Mitral Valve Area
MVG	Transvalvular Mitral Valve Gradient
MVI	Mitral Valve Index
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PHT	Pressure Half-time
PP	Per Protocol
QOL	Quality of Life
RCT	Randomized Controlled Trial
REALISM	Continued Access Study for the MitraClip: includes surgery and high risk arms
REALISM HR	High surgical risk arm of the REALISM Continued Access study
RF	Regurgitant Fraction
RNT	Randomized Not Treated
RV	Regurgitant Volume
SAP	Statistical Analysis Plan
SF-36 QOL	Short Form Quality of Life questionnaire (36 questions)
SGC	Steerable Guide Catheter
SLDA	Single Leaf Device Attachment
SLADd	Septal-Lateral Annular Dimension Diastole
SLADs	Septal-Lateral Annular Dimension Systole
STS score	Society of Thoracic Surgeons
TEE	TransEsophageal Echocardiogram
TIA	Transient Ischemic Attack
TEE	TransEsophageal Echocardiogram
Trimmed Duke Cohort	527 Duke high surgical risk patients treated with medical management trimmed for matched comparison to MitraClip High Surgical Risk patients in the Duke Analysis
TTE	TransThoracic Echocardiogram
UCB	Upper Confidence Bound
UCSF	University of California at San Francisco
VAD	Ventricular Assist Device

1.0 Executive Summary

Unmet Clinical Need in Mitral Regurgitation

With at least 250,000 patients diagnosed with clinically significant mitral regurgitation (MR) (symptomatic with MR severity of 3+ or 4+) each year, MR is the most common type of heart valve disease in the United States⁹. Patients with MR are at risk of poor quality of life, marked limitation in activity, repeated heart failure hospitalizations, and increased mortality. Onset of MR initially leads to impaired hemodynamics, which subsequently results in left ventricular remodeling, which in turn causes worsening MR. Thus, a self-perpetuating cycle of MR is initiated. Although mitral valve repair or replacement surgery is currently standard of care, some patients with clinically significant MR are at an unacceptable risk of morbidity and mortality, and are therefore not offered surgery.^{4, 5, 16, 18, 20}

Patients who are judged at high risk for surgical complications because of underlying conditions are less likely to be referred for surgery or likely to have a surgeon decline to perform surgery due to their risk status. Medical management of clinically significant MR, such as beta blockers and ACE inhibitors, may reduce symptoms by improving fluid build-up and blood pressure³, however, medical management fails to achieve mechanical reduction of mitral regurgitation¹. These individuals experience progression of heart failure and live an uncomfortable life until they progress to death.

Given the significant extent of illness and the debilitating effect on quality of life for patients with clinically significant MR and the lack of effectiveness of medical management, there is a significant unmet clinical need for a valve procedure which effectively decreases the regurgitant volume with reduced morbidity and mortality compared to surgery. The MitraClip therapy offers a percutaneous option for patients with significant morbidity and mortality risk from mitral valve surgery. Through minimally invasive mechanical reduction of MR, the MitraClip therapy addresses a significant unmet clinical need for symptomatic patients facing concurrent challenges of multiple serious comorbidities, including advanced age, compromised ejection fraction, prior cardiac surgery, renal disease, atrial fibrillation and chronic obstructive pulmonary disease (COPD).

Introduction

Over the last 10 years, Abbott Vascular has collaborated with FDA to design clinical trials to establish the safety and effectiveness of the percutaneous MitraClip Device. The MitraClip Clip Delivery System allows for placement of the MitraClip Device to reduce mitral regurgitation (MR) by improving coaptation of the mitral valve leaflets. The MitraClip can be used in MR of functional or degenerative etiologies.

More than 1200 patients have been treated with the MitraClip procedure in US prospective clinical trials, with more than 900 patients having completed a minimum 1-year follow-up, representing 1862 total patient years of follow-up. The MitraClip has been approved in more than 40 countries, and more than 8000 patients have undergone the MitraClip procedure worldwide. The majority of experience with the MitraClip is in high surgical risk patients.

This briefing book presents the body of valid scientific evidence supporting the safe and effective use of the MitraClip Clip Delivery System in high surgical risk patients. Abbott Vascular proposes the following indication for the MitraClip in the US:

The MitraClip® Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation ($MR \geq 3+$) in patients who have been determined by a cardiac surgeon to be too high risk for open mitral valve surgery and in whom existing co-morbidities would not preclude the expected benefit from correction of the mitral regurgitation.

Further information of terms included in the indication statement is provided for clarity. Symptomatic status is determined by NYHA Functional Class of II, III or IV. Mitral regurgitation $\geq 3+$ is determined by an echocardiogram utilizing published methods defined by the American Society of Echocardiology guidelines on determination of MR severity. Too high risk for surgery is a finding by a cardiac surgeon with experience in mitral valve surgery that the risks to the patient from mitral valve surgery, including mortality and major morbidity, are greater than the potential benefit the surgery may provide, and therefore surgery is not recommended. The MitraClip studies defined high surgical risk as predicted risk of surgical mortality of 12% or greater. For context, data from the Society of Thoracic Surgeons registry show that 95% of all isolated mitral valve surgeries from 2008-2012 occurred in patients with a risk of surgical mortality of less than 12%. These data clearly demonstrate that the vast majority of patients with a surgical mortality of 12% or greater are not considered by most surgeons to be candidates for MR surgery.

Overview of MitraClip System

The MitraClip Device is percutaneously implanted. The MitraClip System is used to implant the device and is comprised of the Clip Delivery System (CDS) and Steerable Guide Catheter (SGC). The Clip Delivery System is introduced transvenously through the Steerable Guide Catheter that includes a dilator. Both the Clip Delivery System and Steerable Guide Catheter are actuated by control knobs, levers and fasteners located on the handles. The MitraClip Device can be repeatedly opened, closed and repositioned on the mitral valve leaflets in order to optimize leaflet insertion and MR reduction. The operator may choose to place one or two MitraClip devices to achieve final MR reduction. Additionally, the MitraClip procedure preserves the option for future percutaneous intervention or surgical procedures should the patients risk status improve or emergent procedures be warranted.

Overview of MitraClip Clinical Program

The premise for the MitraClip was a percutaneous approach to the reduction of MR. To this end, Abbott Vascular sponsored a program of clinical studies to evaluate the safety and effectiveness of the MitraClip therapy.

The EVEREST I trial enrolled 55 patients in the US from July 2003 to February 2006 and 5 year follow up was completed in October 2011. The study affirmed feasibility of the percutaneous approach to MR reduction with the MitraClip. The majority of patients (89%) had the device successfully implanted with successful reduction of MR to 2+ or less achieved in 70.9% of patients at discharge. In addition, low rates of adverse events supported the overall safety of the device. In patients with follow-up to 5 years, MR reduction to $\leq 2+$ was durable and was accompanied by reverse left ventricular remodeling and clinically meaningful improvements in NYHA Functional Class.

Since MitraClip was a first in class percutaneous therapy for the treatment of MR, at the time the randomized trial was designed in 2003 it was believed to be important to compare the safety and effectiveness of the MitraClip device to mitral valve surgery which represents the standard of care for MR. Thus, to confirm the safety and effectiveness of the MitraClip, Abbott Vascular sponsored a pivotal randomized comparison (EVEREST II RCT) of the MitraClip to open arrested cardiac surgery for repair or replacement of the mitral valve in surgical candidates. The EVEREST II RCT randomized 279 patients (184 MitraClip, 95 surgical Control) in North America. The premise of the trial was that effectiveness would be lower than for the surgical control by a margin of decreased effectiveness, but the safety would be superior.

The EVEREST II RCT primary safety endpoint was a 30-day major adverse event (MAE) composite. The proportion of patients experiencing the MAE composite in the MitraClip group was compared to that in the surgical Control group using pre-specified margins of superior safety of 2% and 6% for the Intent-To-Treat (ITT) and Per Protocol (PP) populations, respectively. In the ITT analysis, the MAE rate at 30 days was 15.0% for the MitraClip group and 47.9% for the surgical Control group, an observed difference of 32.9% (97.5% UCB=20.7%, $p<0.0001$). In the PP analysis, the MAE rate at 30 days was 9.6% for the MitraClip and 57.0% for the surgical Control group, an observed difference of 47.4% (97.5% UCB=34.4%, $p<0.0001$). The safety endpoint was met by a significant margin.

The EVEREST II RCT primary effectiveness endpoint was Clinical Success defined as freedom from surgery or re-operation, death and MR $>2+$ at 1 year. In the ITT analysis, the Clinical Success rate was 67.4% for the MitraClip and 73.0% for the surgical Control group.

In the PP analysis, the Clinical Success rate was 72.4% for the MitraClip and 87.8% for the surgical Control group.

Since mitral valve surgery achieves MR of $\leq 1+$ most often, FDA believed that $1+$ MR was a more appropriate effectiveness endpoint. Therefore, the effectiveness analyses were also performed using a revised definition of Clinical Success as freedom from surgery or re-operation, death and MR $>1+$ at 1 year. There was a 23.6% difference for the ITT population and a 23.8% difference for the PP population for surgery compared to MitraClip. With this definition of Clinical Success as MR $\leq 1+$, the confidence bounds did not meet the margins of reduced effectiveness, therefore the primary effectiveness endpoint was not met.

After initiation but prior to completion of the EVEREST II RCT enrollment, FDA suggested a study of high surgical risk patients as an important complement to the randomized study that could be considered adjunctive to the EVEREST II RCT and not in isolation. A separate protocol was developed with defined high surgical risk eligibility criteria and the IDE was amended in October 2006 to include the single-arm EVEREST II High Risk Registry (EVEREST II HRR) to run in parallel with the EVEREST II RCT. While there was considerable discussion on the definition of success in the RCT population, FDA agreed that “for the High Risk Registry (HRR), a sustained $\leq 2+$ MR at 1 year is an appropriate end point for this group of patients”.

The EVEREST II HRR enrolled 78 high surgical risk patients of advanced age (mean=77 years) with a high rate of baseline co-morbidities such as prior myocardial infarction, prior stroke, and moderate-to-severe renal disease. The primary objective of the EVEREST II HRR was to assess procedural safety in high surgical risk patients. A secondary objective of the EVEREST II HRR was to assess major effectiveness measures, including changes in left ventricular volumes and dimensions, NYHA Functional Class, SF-36 quality of life score, and rate of heart failure hospitalizations at 1 year compared to baseline. With the exception of heart failure hospitalizations, these endpoints were included to be consistent with the EVEREST II RCT as the benefits of MR reduction were expected to be independent of surgical risk status.

The primary safety endpoint of the EVEREST II HRR was met. The observed procedural mortality rate at 30 days was 7.7% (95.472% UCB = 14.8%) and compared favorably ($p = 0.006$) to the average predicted surgical mortality of 18.2%. The observed procedural mortality rate was also lower when compared to the average STS mortality risk (14.2%).

Significant improvements were observed in left ventricular volumes and dimensions, coupled with reduction in heart failure hospitalizations, improvement in NYHA Class and improvement in quality of life.

After both the EVEREST II RCT and the EVEREST II HRR were fully enrolled, a continued access study (REALISM) of the MitraClip was approved and the study began enrolling patients in 2009. The REALISM Study consisted of two arms, one arm for surgical candidates (same eligibility as the EVEREST II RCT) and a second arm for high surgical risk patients (REALISM HR, same eligibility as EVEREST II HRR). One objective of the REALISM Continued Access study defined in the protocol was the collection of additional safety and effectiveness data to support the marketing application (PMA). Evaluation of pooling was defined in the REALISM protocol for this purpose.

The PMA for approval of the MitraClip Clip Delivery System in both surgical candidates and high surgical risk patients was submitted to FDA in March 2010 supported by data from both the EVEREST II RCT and EVEREST II HRR studies. FDA issued a major Deficiency Letter on July 7, 2010 to which Abbott Vascular provided responses on September 2, 2010, December 15, 2010, March 4, 2011 and June 10, 2011.

After significant discussion with the FDA and consultation with physician advisors, as the EVEREST II RCT demonstrated that MitraClip did not achieve clinical success of $\leq 1+$ MR as completely as surgery, it was determined that the benefit to risk profile of MitraClip did not warrant diverting surgical candidates away from the proven surgical therapy. Abbott Vascular subsequently limited the proposed indication for the MitraClip to patients too high risk for mitral valve surgery. This patient population has an unmet clinical need for a treatment option in that there is no approved medical therapy for MR reduction and these patients are too high risk for mitral valve surgery. The PMA was amended on April 22, 2011 seeking a narrowed indication in high surgical risk patients and providing an analysis of integrated data of 211 patients from the EVEREST II HRR (n=78) and the REALISM HR studies (n=133) to demonstrate the safety and effectiveness of the MitraClip in high surgical risk patients.

A propensity matched analysis was conducted to provide a comparator for these 211 patients to compare mortality with that from a historical cohort of high surgical risk patients with MR severity of 3+/4+ from the Duke Cardiovascular Database treated non-surgically with medical management. Mortality rates at 1 year in the matched cohort of 211 MitraClip and 211 Duke patients were 24.1% and 31.2%, respectively. These analyses demonstrated mortality at 1 year in patients treated with MitraClip was comparable to the natural history of the disease (hazard ratio from adjusted analysis: 0.69, 95% confidence interval: (0.46, 1.04), log-rank p = 0.08). Therefore, in the worst case, the upper confidence bound of 1.04 represents a tolerable mortality risk compared to the natural history of the disease for a high surgical risk population with limited treatment options for MR reduction.

The PMA was amended on August 27, 2012 to include an additional 140 REALISM High Risk patients for a total of 351 patients (n=78 EVEREST II HRR, n=273 REALISM HR) with follow-up through 1 year for an Integrated High Surgical Risk Cohort (Integrated HSR Cohort). The Amendment also included 2-year follow-up data in the original 211 patients.

The primary safety endpoint of the EVEREST II HRR was re-evaluated for the Integrated High Surgical Risk Cohort. The procedural mortality rate of 4.8% was significantly smaller than the predicted surgical mortality of 18.2%. The procedural mortality rate was also lower when compared to the average STS mortality risk (11.3%). At the time of enrollment in the HRR, STS version 2.52 was available and the only option was mitral valve replacement. Mitral valve repair (“reconstruction with annuloplasty”) became an option in STS version 2.6.1. To maintain consistency with the HRR and for the reasons stated above, STS scores in REALISM continued to be calculated for mitral valve replacement.

Use of the STS score is an important consideration in evaluating the composition and outcomes of the Integrated High Surgical Risk Cohort. STS scores for the Integrated High Surgical Risk Cohort were calculated for mitral valve replacement. Evidence supports that in high risk patients, despite anatomic features that make the valve amenable for repair, the vast majority of patients in fact undergo mitral valve replacement. The anatomic eligibility criteria for HRR and REALISM may select patients where surgical repair may be favored over replacement, however, anatomic features are not the only determinant of whether the patient receives surgical mitral valve repair vs replacement. This is supported by the STS database which reports that in 3,213 patients entered in the database from 2008-2012 with an STS score of 12% or greater, 85% of patients underwent mitral valve replacement, whereas the overall rate of mitral valve replacement in the STS database is much lower, (~50%¹⁰). Patients in the High Surgical Risk Cohort with STS \geq 12% represent the top 5% of risk in the STS database. In addition, the surgical literature reports that for complex, high risk patients, survival after repair and replacement is similar. Two references for this are:

- Gillinov et al (J Thorac Cardiovasc Surg 2008;135:885-93) “It is reasonable to perform valve repair in elderly patients with complex degenerative mitral valve pathology because it can eliminate the need for anticoagulation and risk of prosthesis-related complications. However, when valve pathology is so complex that repair is infeasible, this study demonstrates that valve replacement does not diminish long-term outcomes.” This article also states, “In an institution where mitral valve repair is distinctly preferred, patients undergoing valve replacement rather than repair for degenerative MR are older and sicker, with complex mitral valve pathology and multiple comorbidities. Both groups, however, experienced long-term survival commensurate with that of the general population. At this end of the spectrum, survival and freedom from mitral valve reoperation were similar after repair or replacement, including a period of higher early postoperative risk.”

- Gillinov et al (J Thorac Cardiovasc Surg 2001;122:1125-41) “Late survival is poor after surgery for ischemic mitral regurgitation.” Most patients with ischemic mitral regurgitation benefit from mitral valve repair. In the most complex, high risk settings, survival after repair and replacement are similar.

In summary, based on their risk profile, patients treated in the MitraClip high surgical risk studies would have undergone mitral valve replacement at a rate similar to the 85% reported for “like” patients in the STS database. Therefore, use of the mitral valve replacement algorithm in the STS risk calculator is appropriate for determining mortality risk.

Effectiveness measures were re-evaluated in the Integrated HSR Cohort (n=351) to provide additional confidence in the results observed in the EVEREST II HRR. Substantial reductions were observed in patients with either MR of 3+ or 4+, with 46.2% of surviving patients achieving MR \leq 1+ and another 39.7% achieving reduction to MR of 2+, for a total of 85.9% of patients achieving reduction to MR of \leq 2+ (Table 1). Assuming patients who died at discharge without an MR read did not achieve MR reduction to MR \leq 2+, the proportion of patients achieving reduction of MR to \leq 2 was reduced to 85.3%. Table 2 shows that reductions in MR severity to \leq 2+ observed at discharge with the MitraClip Device are substantially durable through 1 year in surviving patients. Assuming patients who died before 1 year did not achieve MR reduction to MR \leq 2+, the durability of MR reduction to \leq 2+ at 1 year was 62.5%.

**Table 1: Integrated HSR Cohort – MR Severity at Baseline and Discharge
Surviving Patients with Paired Data at Baseline and Discharge**

Baseline MR	Discharge MR				Total
	\leq 1+	2+	3+	4+	
1+	1 (50.0%)	1 (50.0%)	-	-	2
2+	23 (53.4%)	18 (41.8%)	2 (4.6%)	-	43
3+	95 (47.7%)	79 (39.7%)	17 (8.5%)	8 (4.0%)	199
4+	31 (38.2%)	31 (38.2%)	16 (19.7%)	3 (3.7%)	81
Total	150 (46.2%)	129 (39.7%)	35 (10.8%)	11 (3.4%)	325

**Table 2: Integrated HSR Cohort - MR Grade at Discharge and 1 Year
Surviving Patients with Paired Data at Discharge and 1 Year**

Discharge MR	1-Year MR				Total
	≤1+	2+	3+	4+	
1+	54 (47.0%)	48 (41.7%)	13 (11.3%)	0	115
2+	26 (28.3%)	53 (57.6%)	10 (10.9%)	3 (3.3%)	92
3+	6 (26.0%)	7 (30.4%)	5 (21.7%)	5 (21.7%)	23
4+	0 (0%)	1 (50.0%)	0 (0%)	1 (50.0%)	2
Total	86 (37.1%)	109 (47.0%)	28 (12.1%)	9 (3.9%)	232

Reduction in MR severity from MitraClip therapy resulted in left ventricular reverse remodeling, reduction in heart failure hospitalizations, improvement in NYHA Class and improvement in quality of life. Clinical benefits in the Integrated HSR Cohort and the RCT MitraClip group were similar in magnitude and smaller than that obtained in the RCT Surgery group. This is consistent with the larger degree of MR reduction obtained with surgery. These results suggest that clinical benefit derived from MitraClip therapy is independent of surgical risk. Further, the consistency of the directionality in clinical benefits between MitraClip and surgery confirm the physiologic relationship between mechanical reduction of MR and its benefits. Despite the lack of a parallel comparator group for the Integrated HSR Cohort, the consistency of the results observed with the RCT provides strong evidence of the effectiveness of MitraClip therapy.

**Table 3: Integrated HSR Cohort – Comparison of Effectiveness to EVEREST II RCT
MitraClip and Surgery Groups**

Effectiveness Measure	Integrated HSR Cohort (N = 351)	EVEREST II RCT MitraClip Group (N = 178)	EVEREST II RCT Surgery Group (N = 80)
Improvement in LVEDV at 1 year	-18 ± 32 ml	-21 ± 24 ml	-40 ± 36 ml
Improvement in LVESV at 1 year	-8 ± 23 ml	-4 ± 14 ml	-5 ± 21 ml
Improvement in SF-36 PCS score at 1 year	4.8 ± 10.4	4.7 ± 10.1	4.4 ± 10.4
Improvement in SF-36 MCS score at 1 year	5.0 ± 13.0	5.8 ± 9.7	3.8 ± 10.3
NYHA Class III or IV: Baseline → 1 year	82% → 17%	46% → 2%	45% → 13%

In the Integrated High Surgical Risk Cohort, the reductions in left ventricular end diastolic and systolic volumes were greater in patients that achieved MR reduction to either 1+ or 2+ than for the group that continued to have 3+ or 4+ MR at 1 year (Table 4). This finding supports the conclusion that improvements in MR to 1+ or 2+ are associated with significant improvement in reverse left ventricular remodeling.

Table 4: Integrated HSR Cohort - Change in Left Ventricular at 1 Year by MR Patients Surviving at 1 Year with Baseline 3+/4+ MR

Change in Left Ventricular Measurement	1-Year MR		
	≤ 1+	2+	3+/4+
LVEDV, ml			
N	63	77	32
Mean	-26.5	-18.7	-10.5
(95% Conf Int)	(-34.9, -18.2)	(-25.5, -11.9)	(-23.1, 2.2)
LVIDd, ml			
N	68	88	33
Mean	-0.3	-0.2	-0.1
(95% Conf Int)	(-0.4, -0.1)	(-0.3, -0.1)	(-0.2, 0.0)
LVESV, ml			
N	63	77	32
Mean	-13.9	-5.6	-5.4
(95% Conf Int)	(-20.4, -7.4)	(-10.3, -0.9)	(-13.6, 2.8)
LVIDs, ml			
N	66	82	31
Mean	-0.2	-0.0	-0.0
(95% Conf Int)	(-0.4, -0.1)	(-0.1, 0.1)	(-0.2, 0.2)

Safety and Effectiveness Across Development

Procedure time, device time, and fluoroscopy duration all decreased over the course of clinical trial use of the MitraClip. The mean procedure time decreased from 255 minutes to 147 minutes, mean device time decreased from 199 minutes to 113 minutes, and mean fluoroscopy time decreased from 60 minutes to 40 minutes between the EVEREST I Feasibility study and REALISM HR Continued Access Study, respectively. MitraClip implant rates improved over the course of time from 89% in the EVEREST I Feasibility Study (2003) to 93% in the EVEREST II RCT (2005) and 96% in both the EVEREST II HRR (2007) and REALISM HR Continued Access studies (2009 through 2011). The majority (50-60%) of patients received one MitraClip Device, and 27%-39% received two MitraClip Devices to achieve MR reduction across trials. The mean post-procedure length of hospital stay was between 2-3 days across studies. The short recovery period observed is especially important in a high surgical risk elderly population who would otherwise be hospitalized for longer durations after surgery. The majority of both high surgical risk

(87.5%) and surgical candidate (91.5%) patients treated with the MitraClip in the REALISM Continued Access study were discharged home without home healthcare.

A longitudinal assessment of the association of MR reduction with clinical benefit in LVEDV and LVESV, and NYHA Functional Class from baseline to 1 year demonstrated reduction of MR severity to $\leq 2+$ at 1 year resulted in significant decreases of LVEDV ($p < 0.0001$) in both Degenerative MR (DMR) and Functional MR (FMR) patients treated with the MitraClip Device, significant decreases of LVESV ($p < 0.0001$) in FMR patients, and a low likelihood of NYHA Class III/IV symptoms at 1 year for both FMR and DMR patients. These results demonstrate that across studies, the reduction of MR to $\leq 2+$ with the MitraClip confers significant clinical benefit.

Device and procedure related event rates were low. Single leaflet device attachment (SLDA), defined as the attachment of the MitraClip Device to one mitral leaflet, decreased across trials with an observed rate of 10.2% in the EVEREST I Feasibility study to 1.3% and 2.7% in the EVEREST II HRR and REALISM HR studies, respectively. There were no reported device embolization events in the clinical trials, and a total of 2 cases reported out of >11,000 devices implanted worldwide ($< 0.02\%$). The rate of mitral valve stenosis was low and stable over time, with observed rates of 2.7% and 0.4% in the EVEREST II HRR and REALISM HR studies, respectively.

Additional Clinical Trials

Abbott has recently commenced two trials to gain further knowledge on the subset of patients with symptomatic functional MR who are too high risk for surgery and have ongoing heart failure despite optimal medical management; the COAPT trial in the US and the RESHAPE-HF trial in Europe.

The COAPT trial shares many of the same elements as were included in the study protocols resulting in the Integrated High Risk Cohort, such as the same MitraClip Device capable of reducing MR to 2+ or less, an open label trial, use of the STS or surgeon assessment to assess surgical risk. Unique to COAPT is the use of a central eligibility committee to ensure 1) surgical risk is adequately documented by the surgeon investigator when the STS score is less than 8%, and 2) confirmation that the patient has been adequately treated for heart failure. The trial will randomize 420 patients (210 MitraClip and 210 medical therapy) with a primary effectiveness endpoint of recurrent heart failure hospitalizations. The COAPT trial is intended for further advancement of the knowledge of the therapy and improving the clinical understanding of the benefits of the technology in patients with heart failure. The trial will also generate health economic data and support establishment of treatment guidelines for MitraClip therapy in heart failure patients. The trial was conditionally

approved in February 2012 and as of February 2013, 2 patients have been enrolled. Upon completion, and if successful, the results of the COAPT trial will be submitted to FDA for a specific indication for heart failure in high surgical risk patients.

The RESHAPE-HF trial will be conducted in Europe and will study patients with advanced heart failure and functional MR. This 800 patient trial randomizes patients 1:1 between MitraClip and medical therapy. The primary endpoint is a hierarchical composite of all-cause mortality and recurrent heart failure hospitalizations. The trial will also generate health economic data and support establishment of treatment guidelines for MitraClip therapy for advanced heart failure. The trial will begin enrollment mid-2013.

These large randomized trials show Abbott's commitment to continue to advance the knowledge of the MitraClip therapy in the commercial setting.

MR Reduction with the MitraClip System

The MitraClip Device reliably reduces MR to 2+ or less, and in many cases to 1+ or less. There has been considerable discussion between FDA and Abbott as to the appropriate threshold for success related to MR reduction; specifically 1+ versus 2+ MR. Abbott agrees with FDA's position that when a patient undergoes surgery, with its associated morbidity, it is imperative to achieve MR reduction to 1+ or less. Therefore, in the trial randomizing MitraClip against the "gold" standard, surgery, MR reduction to 1+ or less was considered by FDA to be an appropriate success criterion. However, early in the conception of the High Risk Registry, FDA communicated that reducing MR to 2+ or better at a year was appropriate for the high surgical risk population. After the High Risk Registry was completed and after the original PMA was filed (March 2010), FDA communicated that 1+, not 2+, was their criterion for success. Abbott remains confident that the trial results and the medical community support the reduction of MR to 2+ or less in these high surgical risk patients as an acceptable result in high surgical risk patients.

MR is a surrogate mechanistic measure of the performance of MitraClip and is the most common measure provided in the literature for surgical outcomes. In the Integrated High Surgical Risk Cohort, the endpoints for effectiveness were defined as the clinical outcomes expected with MR reduction rather than MR reduction alone, namely: reduction in left ventricular size, improvement in NYHA, improvement in quality of life and reduction in heart failure hospitalizations. All of these endpoints showed significant improvement from baseline at 1 year after MitraClip. The data also indicate that MR reduction to either 1+ or 2+ provides clinical benefits. Table 3 shows that surgery provides more reduction in left ventricular size than the MitraClip, and this is consistent with the fact that surgery reduces MR to 1+ or less more often than MitraClip. Table 4 shows that MR reduction to 2+ also

shows significant reduction in left ventricular size following MitraClip. These data support a definition of effectiveness of MR reduction to 2+ or less in patients that are too high risk for surgery.

It should be noted that with more than 50 years of surgical literature, data from only one retrospective non-randomized evaluation of 81 patients who underwent surgery from 1993 to 2001 exists to support the assertion that 1+ MR should be the definition of success in patients too high risk for surgery (Maisano, J Thorac Cardiovasc Surg 2003;126:1987-97). The population presented by Maisano et al. included patients with rheumatic disease (7.5%) and severe annular calcification patients (46%), both of which were exclusions for treatment with MitraClip. The authors state that “excluding patients with annular calcification, rheumatic disease and edge-to-edge repair as a rescue procedure, only 1 of 42 patients needed re-operation in the follow-up period compared with 8 of 37 patients with these risk factors ($p = 0.005$).” Maisano et al. also compared outcomes (rehospitalization rates) in patients with 0-1+ MR with patients with 2-4+ MR. There were 14 patients reported with MR 2-4+ and 3 (21%) of these had MR of 3+. Therefore, the reported outcomes include patients with 3+ MR along with 2+ MR. It is difficult to draw conclusions when patients with 3+ MR are included in the analysis. A subsequent paper by Maisano (Maisano, et al. Eurointerv, 2006; 2:181-186) reported freedom from the combined endpoint of re-operation and recurrence of MR>2+ of $90\% \pm 5\%$ at 5 years with the Alfieri technique.

In summary, reduction of MR to 2+ or less is an appropriate success criterion for patients too high risk for mitral valve surgery and provides significant clinical benefits.

Narrowing of Indication to High Surgical Risk Patients

The initial approach to establishing safety and effectiveness of the MitraClip device was the design and conduct of a randomized pivotal trial for the novel technology. This trial was randomized to the gold standard of care for MR reduction – mitral valve repair or replacement surgery. At the time of this first trial, the safety profile and level of effectiveness of the device were unknown, including how often patients would require surgery following treatment. Therefore, this first study was conducted in patients who could undergo surgery if needed, i.e. surgical candidates. The randomized trial confirmed the mechanistic capability of the device to grasp and coapt the leaflets on a beating heart resulting in reduced MR to 2+ or less in the large majority of patients. This first generation of the novel MitraClip technology was able to reduce MR to 2+ or less in about 75% of patients, but only able to reduce MR to 1+ in around one-third of patients. The level of MR reduction was less than observed for surgery where $\leq 1+$ MR was achieved in most cases. As expected from a percutaneous procedure, there was a lower rate of complications from the

MitraClip procedure and MitraClip patients also had shorter recovery times in comparison with the surgical group. However, these safety advantages were offset by the diminution of MR reduction compared to surgery. This led to the conclusion that patients who are candidates for surgery should continue to receive the gold standard of care; namely mitral valve surgery. Based upon the realization that the EVEREST II RCT results would not support diversion of surgical candidates to the less invasive alternative, Abbott Vascular decided to continue to pursue only a proposed indication for the MitraClip in patients too high risk for mitral valve surgery.

During enrollment of the randomized trial, FDA suggested the design of a single-arm study in high surgical risk patients to complement the randomized trial. At that time, the results of the randomized trial were still unknown. The Agency provided guidance that reduction of MR to 2+ or less sustained through one year follow-up was an appropriate effectiveness endpoint for high surgical risk patients. Abbott collaborated with FDA to design and enroll a single arm high surgical risk study, known as the EVEREST II High Risk Registry (EVEREST II HRR).

The EVEREST II HRR dataset was derived from an approved protocol with pre-specified endpoints and analysis plan.

The HRR demonstrated that the MitraClip procedure was well-tolerated in patients too high risk for surgery. Procedural mortality was lower than the predicted risk of surgery and significant improvements in multiple measures of clinical benefit were shown over baseline. Support for use of MitraClip in these high surgical risk patients was further bolstered by a subsequent subgroup analysis of the randomized trial, which showed that patients who tended to be at higher risk (such as the elderly patients, patients with lower EF and patients with Functional MR etiology) had similar effectiveness in reducing MR to 2+ or less as surgery.

Having concluded that surgical candidates should not be diverted from the proven surgical therapy and having demonstrated superior safety of MitraClip to surgical mortality in high surgical risk patients, it was determined that the indication for approval should be narrowed to include only high surgical risk patients who had no other option for MR reduction.

Abbott took several steps to consolidate available clinical data to support a finding of reasonable safety and effectiveness of the MitraClip device for the proposed indication in patients too high risk for surgery, including:

- First, results of the 78 high surgical risk patients from the EVEREST II High Risk Registry

- Second, while the randomized trial was not for the specific high surgical risk indication, Abbott Vascular diligently completed this challenging to enroll trial and has completed over 3 years of follow-up, with follow-up to 5 years ongoing. These data provide important randomized outcomes on the mechanistic capability of the device as well as a surgical comparator, albeit in non-high risk patients. Completion of 3-year follow-up in the HRR in conjunction with 3-year follow-up in the randomized trial allows the evaluation of durability of the lower degree of MR reduction obtained acutely with MitraClip, and the consequent clinical benefits.
- Third, additional data continued to be collected in a continued access protocol, called REALISM. REALISM was designed to further collect information regarding use of the MitraClip System in addition to providing additional safety and effectiveness data in support of the pre-market approval application (PMA). At the time of preparing for Advisory Panel, 273 additional high surgical risk patients had completed 1 year follow-up. Results through 1 year on a total of 351 high surgical risk patients treated with the MitraClip are reported in support of the safety and effectiveness of the MitraClip device for the proposed indication.

Pooling of the HRR and REALISM patients was described in the REALISM protocol and resulted in the Integrated High Surgical Risk Cohort. The analyses that were carried out on the Integrated High Surgical Risk Cohort were identical to those specified in the HRR protocol, however, the size of the pooled Integrated High Surgical Risk Cohort was not pre-specified.

- Fourth, recognizing the absence of a controlled comparator, Abbott identified a large cardiovascular database (Duke University) with patient-level data that included MR severity and baseline comorbidities necessary to propensity match to the MitraClip high surgical risk patients. A statistical analysis plan was written and finalized prior to analysis. Statisticians from Duke independently completed the propensity analysis comparing high surgical risk patients who had undergone the MitraClip with high risk patients in the Duke database, allowing comparison of 30-day and 1-year mortality.

While a randomized controlled trial on the narrowed indication would be preferred, adequate data have been collected that meet the level of valid scientific evidence to support a high surgical risk indication. Per FDA's guidance on determination of benefit to risk, novel technologies that fill an unmet need may be found reasonably safe and efficacious through the use of comparators short of a randomized trial. Specifically, a patient level comparator is cited as valid scientific evidence. Additionally, for novel technologies the guidance contemplates: "devices representing or incorporating new technologies, especially those that are first-of-a-kind, may provide a less than optimal benefit, but may also offer advantages that did

not previously exist. With subsequent iterations of the device its benefit-risk profile may improve, the expected level of safety and effectiveness may increase, and later versions may offer significant advantages over the initial device. In these circumstances, we may approve a device with less benefit or more risk than would be generally tolerated for more established technologies, particularly where providers and patients have limited alternatives available, to facilitate patient access and encourage innovation.”

Abbott Vascular recognizes that the Integrated High Surgical Risk Cohort is adjunctive to the randomized controlled trial, however it was conducted under a protocol with pre-specified endpoints, pooling and analyses. Although the randomized trial fell short of supporting use of MitraClip in surgical candidates, it benchmarked the safety, effectiveness and durability of the MitraClip against the gold standard (surgery).

Patients who are too high risk for mitral valve surgery have no other therapeutic option. Medications are not indicated or approved for MR reduction. They may provide symptom relief, but even with medications many patients continue to live with the debilitating effects of MR and often become refractive to medications. There exists a large unmet clinical need for these patients suffering from MR. Timely PMA approval of MitraClip will provide an option for these patients so that they may live with improved quality of life, fewer hospitalizations for heart failure and reduced symptoms of MR. Recognizing that more than 8000 patients have been treated worldwide with positive safety and efficacy signals, the totality of the data establish a reasonable assurance of safety and effectiveness of the MitraClip for the proposed indication. These data in the PMA are provide a reasonable assurance of safety and effectiveness to support a high surgical risk indication in the United States at this time rather than waiting another 4-5 years for additional studies to be completed.

Post Approval Commitments

Abbott Vascular is committed to ensure excellent patient outcomes through responsible controlled roll-out of the MitraClip therapy. This includes commitment to selection of appropriate treatment centers, delivery of a robust training program and implementation of a post approval program.

MitraClip commercialization efforts will be restricted to heart centers with a multi-disciplinary heart team comprised of an experienced cardiac surgeon, an implanting physician (if it is not the cardiac surgeon) and an echocardiographer all of whom are required to assess patient suitability for each procedure. It is anticipated that up to 150 centers will be trained in the first year of commercialization.

Abbott Vascular has developed a detailed training program for the heart team with a focus on the MitraClip System, patient screening and selection, and procedure training. The training materials provide extensive information on patient screening to ensure that only suitable candidates for the MitraClip are identified per product labeling, including evaluation of patient MR severity, surgical risk status, and mitral valve anatomy. The heart team is trained on device preparation and step-by-step procedural use. Abbott will provide procedural support including pre-procedural patient selection and procedure proctoring during the training period. Continuing education will also be provided. The training materials also include an optional simulation program tool called the MitraClip Virtual Procedure (MVP) which provides an additional means for the heart team to practice the procedural steps and virtually manipulate the MitraClip System, the echo probe and simultaneously see the relative positions of MitraClip in a 3-dimensional view of the heart, a 2-dimensional view on echocardiogram and a fluoroscopy view.

Abbott Vascular is committed to a comprehensive post-approval clinical program. All patients enrolled in US IDE pre-approval studies will complete follow-up through 5-years. Additionally, Abbott Vascular is working in active partnership with both ACC and STS to ensure that all commercial patients in the United States will be enrolled in a National MitraClip Registry as part of the Transcatheter Valve Therapy (TVT) registry. The continued collection of registry data will allow for ongoing monitoring of clinical outcomes data. Furthermore, Abbott Vascular is working with FDA to design a Post Approval Study nested within the TVT Registry which will be launched when the MitraClip is approved for commercial use and study approval is received. The Post Approval Study is expected to be a prospective, single-arm, multicenter study of approximately 2400 patients enrolled in accordance with the labeled indication and including follow-up through 5 years.

Benefit-Risk Conclusion

Standard of care treatment for clinically significant mitral regurgitation is mitral valve surgery. Patients at too high risk for mitral valve surgery have limited treatment options. These patients are often offered only medical management for palliative care. Medical management does not reduce MR or prevent further decline in cardiovascular function or increase survival.

The MitraClip Device reduces mitral regurgitation through a percutaneous approach without the need for cardiac arrest. Relatively short procedure times and low device complication rates support its safe use. In the Integrated High Surgical Risk Cohort, approximately 86% of surviving patients and approximately 62% of all patients experienced MR reduction, accompanied by meaningful improvements in left ventricular function, quality of life, NYHA Class symptoms and heart failure hospitalization rates. The magnitudes of clinical benefits

were similar in males and females, and in patients with DMR or FMR. The MitraClip effect on the measures of clinical benefit in both the Integrated High Surgical Risk Cohort and the RCT MitraClip group, though smaller than surgery, were consistent with the expected benefits from the mechanical reduction of MR. Reduction in MR, favorable LV reverse remodeling and improvement in NYHA Class symptoms were sustained through 2 years. These benefits exceed what may be expected from medical management.

Benefits of the MitraClip Device clearly outweigh the risks of use. The 30 day procedural mortality rate was significantly lower than predicted surgical mortality. Survival at one year was no worse than that observed in a well matched subject level comparator of medically treated patients in the Duke Cardiovascular Database. This provides evidence that mortality is not increased compared to a high surgical risk medically treated population. Adjudicated major adverse events, complication rate and device related safety events were consistent with the patient population and did not suggest any unique risk for the device. Overall safety and post-marketing experience also support safe use of the device. This favorable safety profile is indispensable to the high surgical risk patient niche for whom the risks of conventional surgery and prolonged recovery from surgery greatly outweigh any potential surgical benefits and for whom medical management provides only palliative care.

The appropriate benefit–risk profile in support of this decision will be reinforced by a rigorous post-approval clinical program, a robust training regimen based upon a decade of MitraClip experience, and product labeling refined to ensure safe and effective product use.

The MitraClip therapy offers a unique safety advantage, addresses the distinct treatment needs of a difficult-to-treat patient population, and attains safety rates that are no worse than the currently accepted modality of treatment in a less risky patient population. The totality of evidence based upon premarket data provides a reasonable assurance of safety and effectiveness in the proposed high surgical risk population to support PMA approval of the MitraClip Device.

In conclusion, the MitraClip technology offers a compelling therapeutic option for the high surgical risk patient population, which would otherwise lack a safe alternative to treat MR.

2.0 Introduction

Over the last 10 years, Abbott Vascular has collaborated with FDA to design clinical trials to establish the safety and effectiveness of the percutaneous MitraClip Device. The MitraClip Device is implanted through use of the MitraClip Clip Delivery System and is intended to reduce mitral regurgitation (MR) by improving coaptation of the mitral valve leaflets. The MitraClip can be used in MR of functional or degenerative etiologies.

More than 1,200 patients have been treated with the MitraClip procedure in US prospective clinical trials, with over 900 patients having completed 1-year follow-up, representing 1861.9 patient years of follow-up. Worldwide, the MitraClip has been approved in over 40 countries with more than 8,000 patients treated with MitraClip procedure. The majority of experience with the MitraClip has been in high surgical risk patients and about 67% have had functional mitral regurgitation.

Abbott Vascular proposes the following indication for MitraClip in the United States:

The MitraClip[®] Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR $\geq 3+$) in patients who have been determined by a cardiac surgeon to be too high risk for open mitral valve surgery and in whom existing co-morbidities would not preclude the expected benefit from correction of the mitral regurgitation.

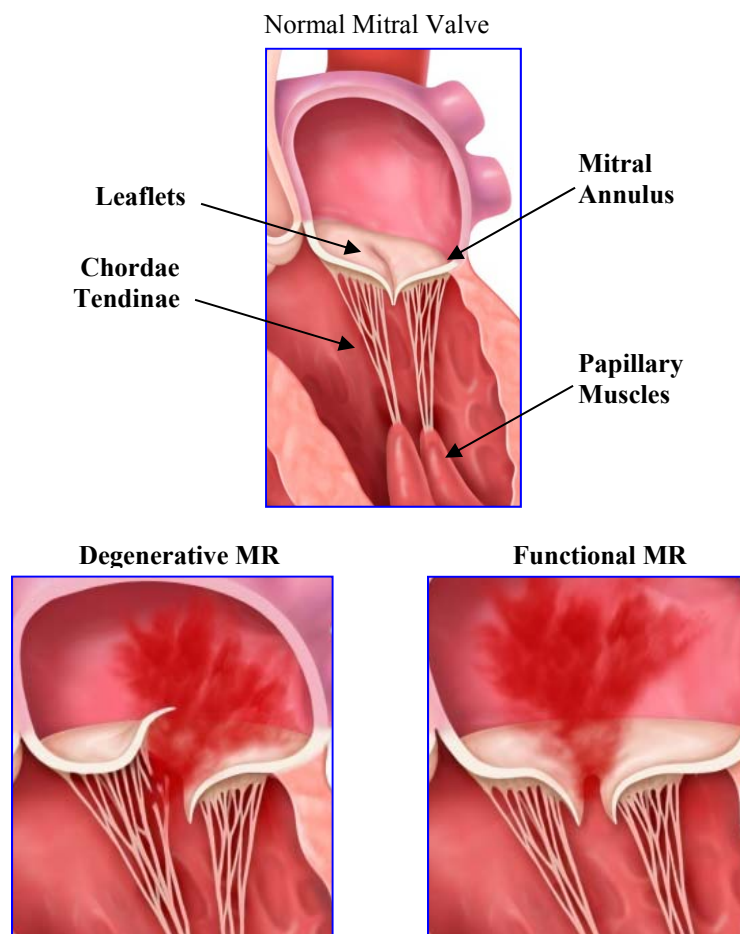
Further information of terms included in the indication statement is provided for clarity. Symptomatic status is determined by NYHA Functional Class of II, III or IV. Mitral regurgitation $\geq 3+$ is determined by an echocardiogram utilizing published methods defined by the American Society of Echocardiology guidelines on determination of MR severity. Too high risk for surgery is a finding by a cardiac surgeon with experience in mitral valve surgery that the risks to the patient from mitral valve surgery, including mortality and major morbidity, are greater than the potential benefit the surgery may provide, and therefore surgery is not recommended. The MitraClip studies defined high surgical risk as predicted risk of surgical mortality of 12% or greater. For context, data from the Society of Thoracic Surgeons registry show that 95% of all isolated mitral valve surgeries from 2008-2012 occurred in patients with a risk of surgical mortality of less than 12%. These data clearly demonstrate that the vast majority of patients with a surgical mortality of 12% or greater are not considered by most surgeons to be candidates for MR surgery.

This briefing book will present the body of valid scientific evidence supporting use of the MitraClip Clip Delivery System based on approved investigational device exemption studies and supported by worldwide experience.

3.0 Mitral Regurgitation Background

Proper opening and closure of the mitral valve requires the coordinated function of multiple anatomic structures including the left atrium (LA) and left ventricle (LV), the mitral valve leaflets, valve annulus, chordae tendineae and papillary muscles (Figure 1). Malfunction of one or more of these structures can cause the mitral valve leaflets to close inadequately, resulting in the backward flow of blood called mitral regurgitation (MR). The two most common causes of MR are degenerative and functional etiologies. Degenerative mitral regurgitation (DMR) is characterized by structural pathology of the valve or sub-valvular apparatus including stretching or rupture of the chordae tendineae, leading to mitral valve prolapse or flail, respectively. In functional mitral regurgitation (FMR), the valve anatomy is normal, however valve function is impacted due to impaired ventricular wall motion and dilatation associated with coronary artery disease or cardiomyopathy.

Figure 1: Mitral Valve and Mitral Regurgitation



Cardiac Surgery in the Adult. New York: McGraw-Hill 2003:987-997

Mitral valve regurgitation is an important cardiovascular disease that is increasing in prevalence. Patients with MR may remain asymptomatic for years. Over time, the retrograde flow of blood back into the left atrium impairs the hemodynamic function of the heart by increasing left atrial pressure and decreasing forward stroke volume and cardiac output. Volume overload is also imposed on the left ventricle. Compensatory left ventricular dilatation initially allows for preservation of cardiac output, however, the LV remodeling leads to papillary muscle displacement, annular dilatation, and leaflet tethering, which ultimately lead to increased MR. When left untreated, MR results in a self-perpetuating cycle of increased MR and ultimately to heart failure symptoms, hospitalizations and death.

Mitral regurgitation is graded on a scale of mild (1+) through severe (4+) (Appendix A). Medical management is instituted for most patients with mild or moderate MR (1+ or 2+). There is, however, no generally accepted effective pharmacologic regimen for patients with MR. Medical management is primarily instituted to mitigate preload, afterload, and hypertension, however; medical therapy is palliative at best. No pharmacologic study has definitively demonstrated improved hemodynamics, a delay in time to surgery or a reduction in mortality with chronic MR.

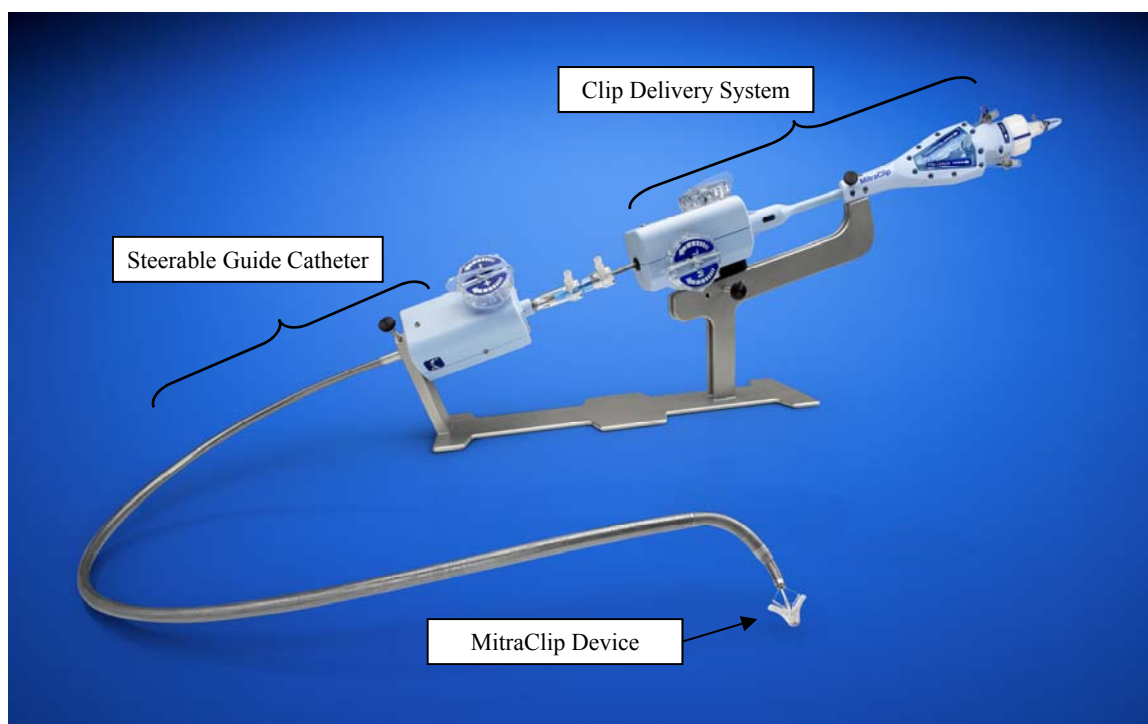
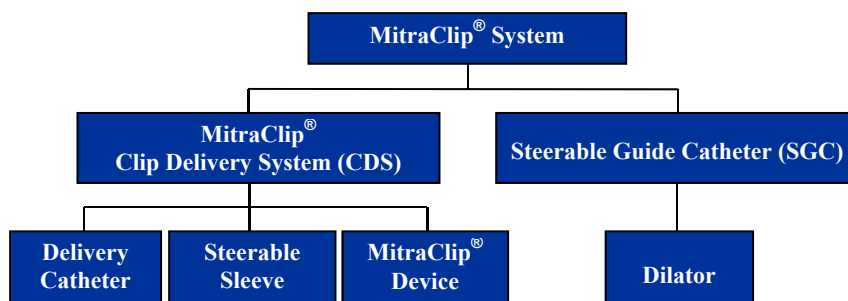
The ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease² recommend intervention for moderate to severe (3+) or severe (4+) MR. Mitral valve surgery (repair or replacement) is generally considered the standard of care for the reduction of MR and is the second leading valvular surgery performed in the U.S. according to figures reported to the Society for Thoracic Surgeon (STS) Database through 2008[†]. Although surgery is effective in reducing MR, there is, however, significant morbidity and mortality associated with mitral valve surgery. Patients that are deemed too high risk to undergo mitral valve surgery currently have no option for the reduction of their MR. Without surgery to repair or replace the mitral valve, heart failure progresses and heart transplant or ventricular assist devices may be considered. Ultimately, patients unable to have surgery can only be offered palliative medical management.

[†] STS U.S. Data Analyses of the Society of Thoracic Surgeons National Adult Cardiac Surgery Database. 2008. www.sts.org.

4.0 Device and Procedure Description

The MitraClip Device is a percutaneously implanted mechanical clip. The MitraClip System is used to implant the MitraClip Device. The MitraClip System (Figure 2) consists of two main components, the Clip Delivery System (CDS) and the Steerable Guide Catheter (SGC). The Clip Delivery System is comprised of a Delivery Catheter, Steerable Sleeve and the MitraClip Device implant on the distal end. The Steerable Guide Catheter includes a dilator and is cleared by the FDA for commercial use introducing cardiovascular catheters into the left side of the heart through the interatrial septum. Both the Clip Delivery System and Steerable Guide Catheter are actuated by control knobs, levers and fasteners located on the handles.

Figure 2: The MitraClip System



The MitraClip Device (Figure 3) is comprised of metal alloys and a polyester fabric (clip cover) commonly used in cardiovascular devices and has two arms that open and close with use of the delivery system handle. The device coapts the mitral valve leaflets resulting in fixed approximation of the leaflets throughout the cardiac cycle, akin to the Alfieri repair technique, yet is placed without the need for arresting the heart or cardiopulmonary bypass (Figure 4).

Figure 3: MitraClip Device (Left side – actual; Right Side –illustration without cover)

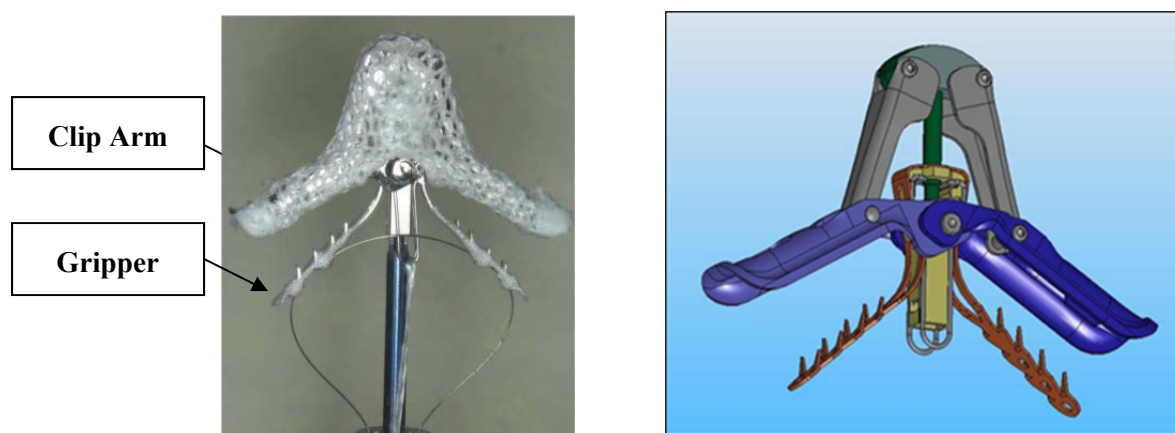


Figure 4: Leaflet Coaptation (Left side – Alfieri Technique; Right Side –MitraClip)

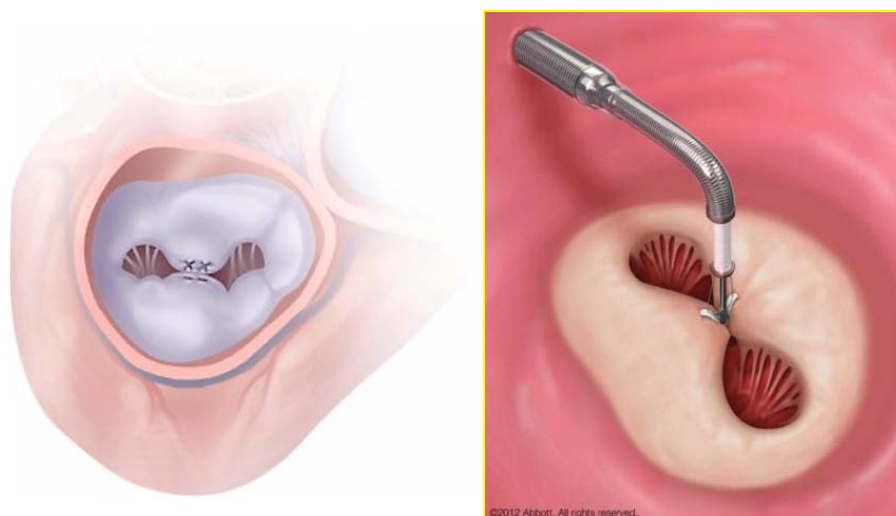


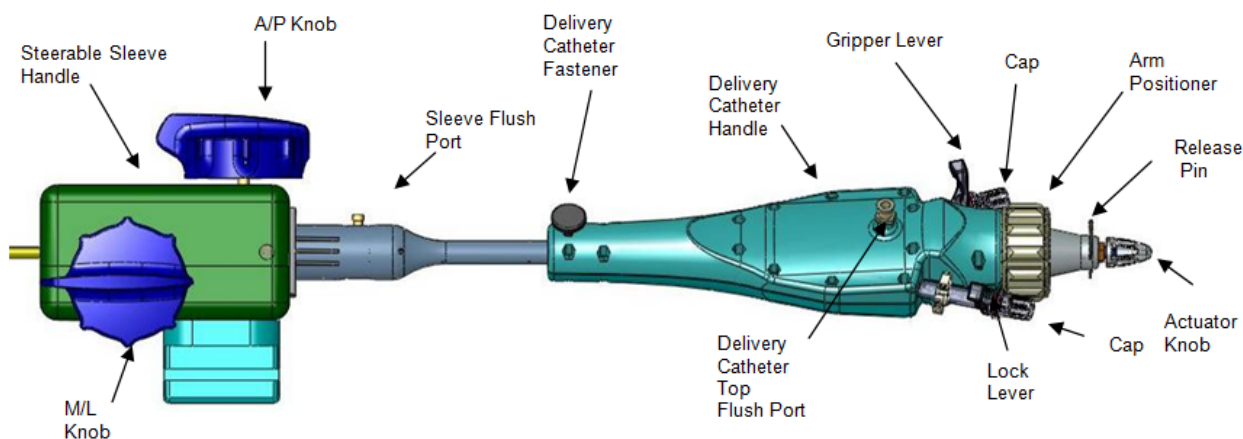
Image: Feldman et al. J Am Coll Cardiol. (2009).

The Delivery Catheter is a 10 Fr, long, flexible hydrophilic-coated multi-lumen shaft secured to the MitraClip Device at the distal end and to a handle at its proximal end. The distal tip of the Delivery Catheter is radiopaque to allow visualization under fluoroscopy and is designed to be securely attached to the MitraClip Device. The 24 Fr Steerable Guide Catheter positions and orients the Clip Delivery System and MitraClip Device in the appropriate location above the mitral valve.

The Delivery Catheter handle and Steerable Sleeve of the Clip Delivery System position, actuate, and deploy the MitraClip Device (Figure 5). The M/L and A/P Knobs on the Steerable Sleeve allow for precise steering of the device in the medial/lateral and anterior/posterior directions. In the Delivery Catheter handle are the Fastener, Lock Lever, Arm Positioner, Actuator Knob, Gripper Lever, and two flush ports. The Fastener temporarily secures the Delivery Catheter position relative to the Steerable Sleeve, to prevent inadvertent manipulation of the MitraClip Device once the leaflets have been grasped. The Lock Lever controls the lock mechanism of the MitraClip Device. The Arm Positioner is used to open and close the clip by advancing and retracting an internal actuator mandrel. The Gripper Lever holds the Grippers in the raised position or releases them to the lowered position during grasping. The Actuator Knob is used to unthread the actuator mandrel resulting in deployment of the Clip. The flush ports are standard female luer fittings that allow for aspiration of air and infusion of liquids into the thru-lumens of the Delivery Catheter.

Figure 5: Clip Delivery System: Delivery Catheter Handle and Steerable Sleeve

The MitraClip procedure is performed under general anesthesia in a catheterization lab using



fluoroscopy and transesophageal and transthoracic echocardiograms (TEE and TTE). The

mitral valve is accessed through a percutaneous transvenous approach via the femoral vein and inferior vena cava. Atrial transseptal puncture is performed and the Steerable Guide Catheter is inserted into femoral vein, advanced over a guide wire and across the intra-atrial septum, and into the left atrium. The Clip Delivery System is then inserted and advanced through the Steerable Guide Catheter in to the left atrium, where the device is steered until it is aligned over the origin of the regurgitant jet. The MitraClip Device Grippers can be raised and lowered and the Clip Arms adjusted to any position from fully open to fully inverted and to fully closed. These positions are designed to allow the MitraClip Device to grasp and approximate the leaflets of the mitral valve.

Adequate reduction of regurgitation is assessed via multiple echo views under beating heart conditions. The MitraClip Device can be repeatedly opened, closed and repositioned in order to optimize leaflet insertion and MR reduction prior to deployment. The MitraClip is then deployed and the Clip Delivery System removed. If needed, a second MitraClip Device can be placed for further MR reduction.

The MitraClip procedure preserves the option for future percutaneous intervention or surgical procedures should the patient's risk status improve or emergent procedures be warranted.

5.0 Overview of the MitraClip Development Program

5.1 Regulatory History and Clinical Development

The MitraClip has been in development for over 10 years in the US and internationally. The MitraClip System received approval for commercialization in the European Union in March 2008 and the MitraClip was recently included in the European Society of Cardiology (ESC) Guidelines on the Management of Valvular Heart Disease as a class IIb recommendation for treatment of MR¹⁷. A two-phase prospective, single-arm, multicenter post-approval observational study of the MitraClip in Europe for the treatment of MR, ACCESS-EU, has completed enrollment. Five hundred sixty seven (567) patients in Phase I and 286 patients in Phase II were treated with the MitraClip in Europe and the study is now in the close-out phase.

Worldwide, the MitraClip is approved in over 40 countries with more than 8,000 patients treated with the MitraClip procedure. Outside the US, the MitraClip System is indicated for “reconstruction of the insufficient mitral valve through tissue approximation”[‡]. The majority of worldwide experience with the MitraClip System has been in high surgical risk patients and about two thirds have functional mitral regurgitation.

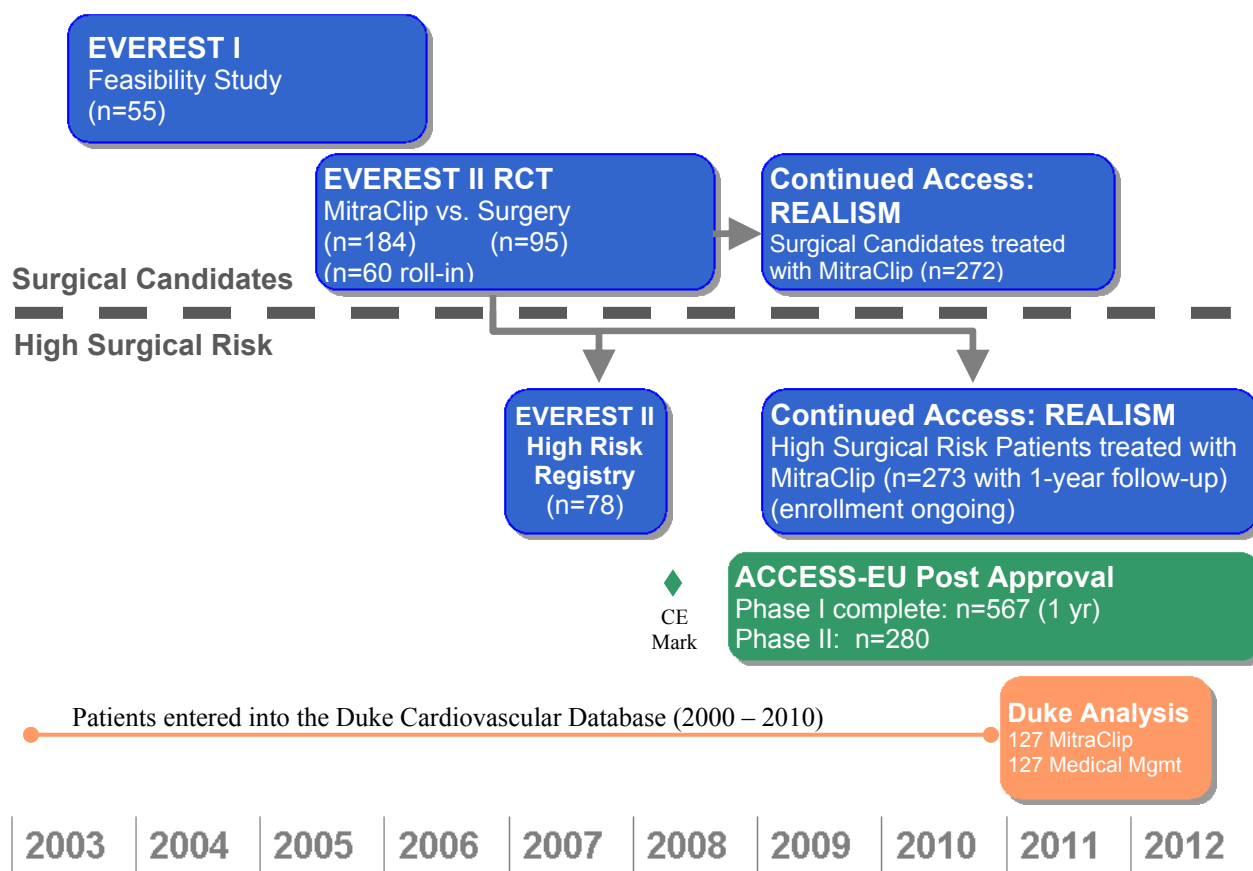
In the United States, the Steerable Guide Catheter received initial FDA clearance in April 2009 for commercial use introducing various cardiovascular catheters into the left side of the heart through the interatrial septum.

Beginning in 2003, Abbott Vascular sponsored a series of clinical studies to evaluate the safety and effectiveness of the MitraClip for the treatment of MR. To date, more than 1200 patients have been treated with the MitraClip procedure in US prospective clinical trials, with over 900 patients having completed a minimum of 1-year follow-up, representing 1861.9 total patient years of follow-up.

[‡] In Singapore, the following text is added to the above indication: “The MitraClip System is intended for patients with moderate [3+] to severe [4+] functional or degenerative mitral regurgitation with symptoms or if asymptomatic, with compromised LV function [ejection fraction <60% or end systolic dimension >45mm]).

An overview of the clinical program is shown in Figure 6.

Figure 6: MitraClip Clinical Program: Enrolled and Treated with 1 year follow-up



The EVEREST I feasibility study was initiated in July 2003 and the final 5 year study follow-up was complete and reported to the FDA in November 2011. The study affirmed feasibility of the percutaneous approach utilizing the MitraClip to reduce MR to $\leq 2+$, the level at which the ACC/AHA Guidelines do not recommend intervention.

The EVEREST II pivotal study, designed as a randomized clinical trial (EVEREST II RCT) of the MitraClip versus mitral valve surgery, was initiated in August 2005. The premise of the trial was that effectiveness would be lower than for the surgical control by a margin of decreased effectiveness, but the safety would be superior. There was considerable discussion between FDA and Abbott Vascular regarding the appropriateness of MR $\leq 2+$ as the success criterion in these surgical candidates. However, the IDE was approved in September 2005 and FDA requested additional analysis of effectiveness outcomes to include MR reduction to

$\leq 1+$ typically achieved by surgery. In this same approval letter, FDA suggested that a single-arm registry of MitraClip in patients considered “high risk” or “inoperable” could be an important complement to the randomized clinical trial.

Accordingly, Abbott Vascular worked interactively with FDA over the next year on design of a protocol for a separate single-arm high risk registry, the EVEREST II High Risk Registry (EVEREST II HRR). The protocol defined high surgical risk eligibility criteria, and was to be conducted as an adjunct to the EVEREST II RCT. An IDE supplement for the conduct of the EVEREST II HRR was submitted in October 2006 and the study initiated in February 2007. The EVEREST II HRR and EVEREST II RCT completed enrollment in January 2008 and November 2008, respectively. The EVEREST II HRR was designed, submitted, initiated and fully enrolled prior to conduct of any data analysis on the EVEREST II RCT. Results of the EVEREST II RCT are provided in Section 5.2.2 and Appendix I. Results of the EVEREST II HRR are further detailed in Section 5.2.2, Section 7.0 and Appendix E, and as part of the Integrated High Surgical Risk Cohort as detailed in Section 8.0 and Appendix G.

In the January 2008 approval letter for the EVEREST II HRR, FDA noted future concerns regarding utility of the data to be generated from this study in determining safety and effectiveness in a PMA application including: the ability of the sample size (estimated at the time to be ~ 50 patients) to sustain hypothesis analysis, heterogeneity of the patient population, experience level of the study surgeons evaluating the high surgical risk status of patients, post hoc data analysis, and the belief that the small high surgical risk dataset was best considered adjunctive to the EVEREST II RCT study and not in isolation as a stand-alone study. Additionally, although reduction of MR to $\leq 2+$ sustained through 12 months was approved as an appropriate endpoint for the high surgical risk population in April 2007, the Agency maintained that reduction of MR to $2+$ may not be a clinically successful outcome, and improvements in secondary effectiveness outcomes and comparison to the RCT were warranted. Abbott Vascular has taken strides with FDA to address each of these concerns, and supportive information is provided throughout this briefing book in conjunction with the associated data presentation.

Following completion of enrollment in the EVEREST II RCT and HRR studies, Abbott Vascular requested Continued Access to the MitraClip Device while the PMA application was prepared and reviewed for approval, as there is public need for the device and there was preliminary evidence of effectiveness with no significant safety concern. FDA granted the request, and the REALISM Continued Access study was initiated in January 2009, with surgical candidates treated with the MitraClip Device followed in one arm and high surgical risk patients treated with the MitraClip followed in another arm (REALISM HR). The REALISM Continued Access study allowed for the collection of additional safety and

effectiveness data in support of the marketing application and to address any new questions regarding the device during the review and approval period.

Each arm of the REALISM study was designed with inclusion/exclusion criteria and endpoints aligned to maintain consistency with the EVEREST II RCT and HRR studies. Eligibility criteria in REALISM HR are identical to EVEREST II HRR, with one exception: patients are excluded from REALISM HR if they had a concurrent medical condition resulting in a life expectancy of less than 1 year. This criterion was added to exclude terminally ill patients, including those in hospice. Safety, effectiveness and follow-up data collection in REALISM HR are identical to EVEREST II HRR, with enrollment and follow-up ongoing through 5 years. REALISM Continued Access patient follow-up presented in this briefing book is complete through 1 year.

The PMA for approval of the MitraClip was submitted to FDA in March 2010 and included the totality of data from both the EVEREST II RCT and EVEREST II HRR studies to support an indication for the MitraClip for reduction of MR. The results from the EVEREST II RCT demonstrated that although the MitraClip can be safely implanted and reduced MR with positive impact on clinical outcomes, surgery provided more complete MR reduction and clinical impact in good surgical candidates. FDA issued a major Deficiency Letter on July 7, 2010 including questions on the adequacy of the effectiveness endpoints incorporating reduction of MR to 2+ or less, safety of the MitraClip Device in high surgical risk patients, and the experience of surgeons evaluating the high surgical risk status of patients in the EVEREST II HRR and *in vivo/in vitro* testing provided in support of the PMA application. Abbott Vascular has provided responses to all questions across four PMA Supplements submitted between September 2010 and June 2011, including 2-year results to address the durability of MR reduction to 2+ achieved with the MitraClip. FDA has indicated that concerns remain regarding design, conduct and analysis of the studies. No additional deficiency letters have been received and the PMA remains under review.

Subgroup analyses of the RCT showed that effectiveness of MitraClip reached parity with surgery in patients with high surgical risk characteristics. After significant discussion with the FDA and consultation with physician advisors, and based upon the realization that the RCT would not support diversion of patients that were surgical candidates to the less invasive alternative, Abbott Vascular decided to narrow the scope of the proposed indication and pursue indication for the MitraClip in only patients too high risk for mitral surgery. This patient population has an unmet clinical need for a treatment option in that there is no approved medical therapy for MR reduction and these patients are not candidates for mitral valve surgery.

The PMA was amended on April 22, 2011 seeking an indication limited to high surgical risk patients. The HR arm of the REALISM Continued Access study collected additional safety and effectiveness data to support the marketing application, and augmented the sample size of the EVEREST II HRR. In the PMA Amendment, data on 211 high surgical risk patients were combined from the EVEREST II HRR (n=78) and the REALISM HR arm (n=133), analyzed and provided to demonstrate the safety and effectiveness of the MitraClip Device in high surgical risk patients. Comparison of these 211 patients to results in the literature on patients managed medically, a concurrent control, and a database of heart failure patients with MR from Ohio State were also provided to support that the MitraClip procedure preserved safety relative to the natural history of the disease. Effectiveness was demonstrated in these high surgical risk patients.

FDA requested additional data to place MitraClip mortality in high surgical risk patients in perspective with the natural progression of the disease. At a Pre-Advisory Panel meeting in May 2011, Abbott Vascular proposed a survival comparison to high surgical risk patients with severe MR managed medically at Duke University Medical Center. This additional post-hoc safety analysis was intended to demonstrate mortality was not worse with MitraClip when compared to high surgical risk patients with MR treated with medical management alone. Propensity matching was used to derive a matched cohort of Duke high surgical risk patients to the 211 MitraClip high surgical risk patients. Data from the survival comparison to the Duke database (Duke Analysis) were submitted to FDA on December 5, 2011. This was followed by a January 20, 2012 meeting to review the Duke Analysis, intended indication for use, and to discuss next steps toward an advisory panel meeting. As enrollment and follow-up in REALISM HR continued, a PMA amendment was filed on August 26, 2012 to update the number of patients reported in the Integrated High Surgical Risk Cohort (Integrated HSR Cohort) with 1-year follow-up (n=351; 78 EVEREST II HRR + 273 REALISM HR), and to include 3-year follow-up in the EVEREST II RCT and HRR studies.

Based upon the revised indication, enrollment in the surgical candidate arm of REALISM was closed to enrollment in September 2011 while enrollment in REALISM HR remains ongoing. Results of the EVEREST II HRR, REALISM HR, the combined Integrated HSR Cohort and comparators to medical treatment are further detailed in Section 8.0 and Appendices D through H.

Overall, Abbott Vascular has submitted 305 Supplements to the original IDE application since 2003, with the majority being requests for compassionate use of the device and other minor modifications to the study protocol, device design or manufacturing process approved by FDA over time. Key regulatory dates for the MitraClip are listed in **Table 5**.

Table 5: Summary of Clinical Study Regulatory History and PMA Submissions

Study	Regulatory Action	Date
EVEREST I, Feasibility	IDE submitted	March 14, 2003
	Conditional Approval Received	April 16, 2003
	Full Approval Received	August 29, 2003
	Study Enrollment	July 2003 – Feb 2006
	5-year Final Study Report submitted	November 17, 2011
EVEREST II, RCT	Pre-IDE meeting with FDA	July 8, 2004
	IDE submitted	August 2, 2004
	Conditional Approval Received	November 3, 2004
	Full Approval Received	September 28, 2005
	Study Enrollment	Aug 2005 – Nov 2008
EVEREST II High Risk Registry	IDE supplement submitted	October 13, 2006
	Conditional Approval Received	November 16, 2006
	Full Approval Received	January 28, 2008
	Study Enrollment	Feb 2007 – Jan 2008
Continued Access (REALISM)	IDE Supplement submitted for Dual Arm Continued Access study (Surgical Candidate Arm and High Surgical Risk Arm)	August 29, 2008
	FDA Conditional Approval Received	November 12, 2008
	FDA Full Approval Received	November 21, 2008
	Study Enrollment – Surgical Candidate Arm	Jan 2009 – Sept 2011
	Study Enrollment – High Surgical Risk Arm	Jan 2009 - ongoing
Submission		
Pre-Market Approval (PMA) Application P100009	PMA filed (broad indication regardless of risk)	March 4, 2010
	Major Deficiency Letter	July 7, 2010
	Responses to July 7, 2010 Deficiency Letter	September 2, 2010
		December 15, 2010
		March 4, 2011
		June 10, 2011
	PMA Amendment to high surgical risk indication only	April 22, 2011
	Pre-Advisory Panel meeting with FDA	May 3, 2011
	PMA Amendment filed with Duke safety comparator, updated clinical data, and request for panel date	December 5, 2011
	Meeting with FDA	January 20, 2012
	PMA Amendment filed with additional patients from Continued Access HR and longer term follow up	August 26, 2012

5.2 Overview of Clinical Program

5.2.1 EVEREST I

The EVEREST I trial (N = 55) affirmed feasibility of the percutaneous approach to MR reduction with the MitraClip. The study included US patients with mitral regurgitation severity $\geq 3+$ determined from a transthoracic echocardiogram (TTE), who were candidates for mitral valve (MV) surgery and cardiopulmonary bypass. The majority of patients (89%, 49/55) in EVEREST I had the device successfully implanted. Successful reduction of MR to 2+ or less as assessed by the Echocardiography Core Laboratory (ECL), the level of MR for which the ACC/AHA guidelines do not recommend intervention², was achieved in 70.9% (39/55) of patients at discharge. The procedure was well tolerated, as patients remained hemodynamically stable throughout the procedure and a low rate of intra-procedural adverse events (3.6%, 2/55) was observed. There were no deaths within 30 days of the procedure, and the majority of continuing patients remain free from death at 5 years (86.4%). MR severity of $\leq 2+$ was observed in 73.3% (11/15) of patients with follow-up through 5 years and was accompanied by left ventricular reverse remodeling and clinically meaningful improvements in NYHA Functional Class. These results indicated that leaflet grasping with the MitraClip device was repeatable, MR reduction was feasible and durable, and provided clinical benefits.

5.2.2 EVEREST II Randomized Controlled Trial

Since MitraClip was a first in class percutaneous therapy for the treatment of MR, at the time the randomized trial was designed in 2003 it was believed to be important to compare the safety and effectiveness of the MitraClip device to mitral valve surgery which represents the standard of care for MR. Thus, to confirm the safety and effectiveness of the MitraClip, Abbott Vascular sponsored a pivotal randomized trial (EVEREST II RCT) of the MitraClip to open arrested cardiac surgery for repair or replacement of the mitral valve in patients with $MR \geq 3+$ who were surgical candidates. The premise of the trial was that effectiveness would be lower than for the surgical control by a margin of decreased effectiveness, but the safety would be superior. The EVEREST II RCT (n=60 roll-in, 184 MitraClip, 95 surgical control) was conducted across 37 North American sites from August 2005 to September 2008, with planned follow-up to 5 years. The trial enrolled both degenerative and functional MR etiologies (73% DMR, 27% FMR). A report on follow-up to 3 years has been submitted in the PMA, and follow-up through 5 years is ongoing.

Multiple clinical endpoints for safety and effectiveness were examined. The EVEREST II RCT primary safety endpoint was a 30-day major adverse event (MAE) composite. The

proportion of patients experiencing the MAE composite in the MitraClip group was compared to that in the surgical Control group using pre-specified margins of superior safety of 2% and 6% for the Intent-To-Treat (ITT) and Per Protocol (PP) populations, respectively.

In the ITT analysis, the MAE rate at 30 days was 15.0% for the MitraClip group and 47.9% for the surgical Control group, an observed difference of 32.9% (97.5% UCB=20.7%, $p<0.0001$). In the PP analysis, the MAE rate at 30 days was 9.6% for the MitraClip and 57.0% for the surgical Control group, an observed difference of 47.4% (97.5% UCB=34.4%, $p<0.0001$).

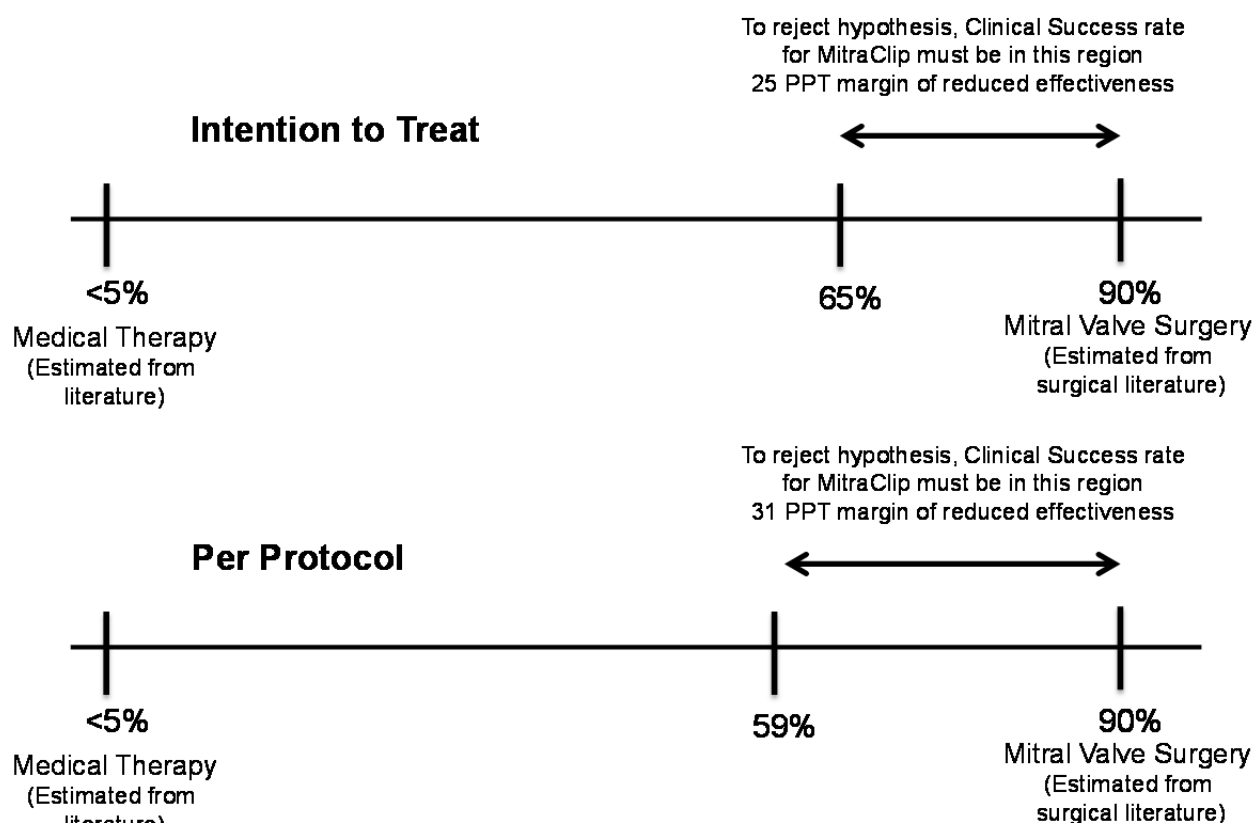
Although the MitraClip group was superior in the primary safety endpoint, a significant component of the safety advantage in MAE rates was the lower rate of transfusions (some of which were for prophylaxis) at 30 days (15.0% MitraClip, 47.9% surgical Control). A sensitivity analysis of the ITT data was performed by substituting major bleeding complications for transfusions (Appendix I) and the primary safety endpoint was still met.

All secondary safety endpoints at 30 days trended in favor of the MitraClip group over surgical Control, with the exception of major vascular complications associated with the percutaneous procedure (4.9% MitraClip, 0% Control).

The mortality rate at 3 years was low and comparable between the MitraClip (12.5%) and surgical Control (14.7%) groups.

The EVEREST II RCT primary effectiveness endpoint was Clinical Success defined as freedom from surgery or re-operation, death and MR >2+ at 1 year. Clinical success rates between the MitraClip and surgical Control groups were compared using a margin of reduced effectiveness of 25 percentage points (PPT) for the ITT population and 31 percentage points for the PP population. The margins of reduced effectiveness selected preserved a substantial proportion (at least two-thirds) of the large surgical effect versus medical management (Figure 7).

Figure 7: Margin of Reduced Effectiveness



Expected Clinical Success Rate

In the ITT analysis, the Clinical Success rate was 67.4% for the MitraClip and 73.0% for the surgical Control group, an observed difference of 5.6% (95% LCB=16.1%, $p < 0.0002$). In the PP analysis, the Clinical Success rate was 72.4% for the MitraClip and 87.8% for the surgical Control group, an observed difference of 15.4% (95% LCB=25.4%, $p < 0.0012$).

The EVEREST II RCT met its safety and effectiveness endpoints.

Since mitral valve surgery achieves MR of $\leq 1+$ most often, FDA believed that $1+$ MR was a more appropriate effectiveness endpoint. Therefore, the effectiveness analyses are also provided using a revised definition of Clinical Success as freedom from MR $> 1+$ at 1 year. There was a 23.6% difference (95% LCB=34.9%, $p = 0.4117$) for the ITT population and a 23.8% difference (95% LCB=37.7%, $p = 0.1692$) for the PP population for surgery compared to MitraClip. With this definition of Clinical Success as MR $\leq 1+$, the confidence bounds did not meet the margins of reduced effectiveness; therefore the primary effectiveness endpoint was not met.

Additional clinical endpoints also supported improved cardiac function in patients treated with the MitraClip. Sequential hypotheses testing of measures of left ventricular function demonstrated statistically significant reductions from baseline to 1 year for both the MitraClip and surgical Control groups in LVEDV (21.3 ml MitraClip, 40.2 ml surgical Control, two-sided $p=0.0003$), LVIDd (0.4 cm MitraClip, 0.6 cm surgical Control, two-sided $p=0.0030$), and LVESV (4.4 ml MitraClip, 5.1 ml surgical Control, two-sided $p=0.7888$), and a trend toward a reduction in LVIDs (0.1 cm MitraClip, 0.0 cm surgical Control). Since MitraClip was less effective at reducing MR than surgery, as expected, measures of change in left ventricular diastolic volumes and dimensions at 1 year from baseline were smaller in the MitraClip group (between-group $p < 0.05$ for LVEDV and LVIDd).

These reductions in left ventricular measures indicate reverse left ventricular remodeling in response to the reduced afterload as a result of the reduction in MR achieved with the MitraClip device or surgery.

The improvement in left ventricular function for both MitraClip and surgery resulted in improvements in NYHA Functional Class and quality of life. The proportion of patients with NYHA Functional Class III or IV decreased from 50.0% of patients at baseline to only 2.4% of patients at 1 year in the MitraClip group and from 45.5% to 12.1% in the surgical Control group. Both the physical component summary (PCS) and mental component summary (MCS) SF-36 quality of life (QOL) scores increased over baseline levels at 1 year in both groups. Both groups experienced improvements in PCS and in MCS scores.

Reduction in MR severity in treated patients in the MitraClip and surgical Control groups was immediate and these results were sustained at 3 years. There was a low rate of re-operation in the surgical Control group (2.6% at 1 year and 5.6% at 3 years). In the MitraClip group, as these patients were surgical candidates, if the MitraClip procedure did not result in significant reduction in MR, patients were converted to mitral valve surgery to achieve the best clinical results. Mitral valve surgery occurred at a rate of approximately 20% at 6 months, with very low rates occurring beyond 6 months for cumulative rates of mitral valve surgery of 21.1% at 1 year and 22.4% at 3 years. Reduction in NYHA Class symptoms were also sustained through 3 years in both groups.

Detailed analyses on the EVEREST II RCT are provided in Appendix I.

EVEREST II RCT demonstrated that MitraClip could be implanted with low complication rates and MR reduction could be successfully and durably achieved. However, the benefit to risk profile of MitraClip in surgical candidates was not optimal. Although the trial fell short of supporting use of MitraClip in surgical candidates, it benchmarked the safety, effectiveness and durability of the MitraClip against the gold standard (surgery).

5.2.3 EVEREST II High Risk Registry

After initiation but prior to completion of the EVEREST II RCT enrollment, FDA suggested a study of high surgical risk patients as an important complement to the randomized study that could be considered adjunctive to the EVEREST II RCT and not in isolation. A separate protocol was developed with defined high surgical risk eligibility criteria and the IDE was amended in October 2006 to include the single-arm EVEREST II High Risk Registry (EVEREST II HRR) to run in parallel with the EVEREST II RCT to evaluate the performance of the MitraClip in patients who were too high risk for mitral valve surgery (see Appendix D for high surgical risk criteria). FDA suggested that the comparison of effectiveness of the MitraClip in the EVEREST II HRR be made to the effectiveness of the surgery in the EVEREST II RCT. The EVEREST II HRR was initiated in February 2007. The study was designed, submitted, initiated and fully enrolled prior to conduct of any data analysis on the EVEREST II RCT.

The EVEREST II HRR study enrolled 78 patients at 25 centers. The primary objective of the EVEREST II HRR was to assess procedural safety in high surgical risk patients. Accordingly, the primary safety endpoint was procedural mortality at 30 days or prior to discharge compared to predicted surgical mortality. Secondary effectiveness measures were similar to those in the EVEREST II RCT, including changes in ECL assessed measures of left ventricular function, NYHA Functional Class and SF-36 quality of life score at 1 year compared to baseline. Rate of hospitalizations for heart failure 1-year pre- and 1-year post-MitraClip was added as a descriptive endpoint for the EVEREST II HRR.

The primary safety endpoint of procedural mortality (observed vs. predicted) was met. The results of the EVEREST II HRR are further detailed in Section 7.0 and Appendix E and as part of the Integrated High Surgical Risk Cohort in Section 8.0 and Appendix G.

5.2.4 REALISM Continued Access Study

After both the EVEREST II RCT and the EVEREST II HRR were fully enrolled, Abbott Vascular requested Continued Access to the the MitraClip Device while the PMA application was prepared and reviewed for approval, as there is public need for the device and there was preliminary evidence of effectiveness with no significant safety concern. FDA granted the request, and the REALISM Continued Access study was initiated in January 2009, with surgical candidates treated with the MitraClip followed in one arm (REALISM NHR) and high surgical risk patients treated with the MitraClip followed in another arm (REALISM HR). The REALISM Continued Access study allowed for the collection of additional safety and effectiveness data in support of the marketing application and to address any new questions regarding the device during the review and approval period. REALISM is closed to

enrollment in the surgical candidates arm and is currently enrolling in the high surgical Risk arm.

Each arm of the REALISM study was designed with inclusion/exclusion criteria and endpoints aligned to maintain consistency with the EVEREST II RCT and HRR studies. Eligibility criteria in REALISM HR are identical to EVEREST II HRR, with one exception: patients are excluded from REALISM HR if they had a concurrent medical condition resulting in a life expectancy of less than 1 year. This criterion was added to exclude terminally ill patients, including those in hospice. Safety, effectiveness and follow-up data collection in REALISM HR are identical to EVEREST II HRR, with enrollment and follow-up ongoing through 5 years. REALISM Continued Access patient follow-up presented in this briefing book is complete through 1 year.

The REALISM Continued Access High Risk arm (REALISM HR) included in this briefing book is a cohort of 273 patients consecutively enrolled at 36 centers and have 1 year of follow-up or withdrew or died. Results of this cohort of patients are further detailed in Appendix F and as part of the Integrated High Surgical Risk Cohort in Section 8.0 and Appendix G.

5.2.5 Integrated High Surgical Risk Cohort

Pooling of EVEREST II HRR (N = 78) and REALISM HR (N = 273) patients resulted in 351 patients referred to as the Integrated High Surgical Risk Cohort (Integrated HSR Cohort). The EVEREST II HRR met pre-specified endpoints and re-analysis of these endpoints with the Integrated HSR Cohort was expected to yield greater precision in the reported estimates of the safety and effectiveness endpoints.

FDA expressed concerns about comparing safety of MitraClip to surgery but effectiveness to medical management (baseline). Upon request from FDA to identify alternative safety comparators, a patient level comparator for mortality (natural history of mitral regurgitation) from the Duke University Medical Center was identified. Abbott Vascular expected to demonstrate that mortality with MitraClip at 1 year was not worse than the natural history of the disease. Mortality rates at 1 year in the matched cohort of 211 MitraClip and 211 Duke patients were 24.1% and 31.2%, respectively. These analyses demonstrated mortality at 1 year in patients treated with MitraClip was comparable to the natural history of the disease (hazard ratio from adjusted analysis: 0.69, 95% confidence interval: (0.46, 1.04), log-rank p = 0.08). A full report, including details on the matching methodology is provided in Appendix H.

5.2.6 ACCESS-EU (European Experience)

The MitraClip System received approval for commercialization in Europe in March 2008, and is indicated for reconstruction of the insufficient mitral valve through tissue approximation. ACCESS-EU was a two-phase prospective, single-arm, multicenter post-approval observational study of the MitraClip in Europe for the treatment of MR. The primary objective of the ACCESS-EU study was to gain information with respect to health economics and clinical care, and to provide further evidence of safety and effectiveness. Five hundred sixty seven (567) patients in Phase I and 286 patients in Phase II were treated with the MitraClip in Europe. The study is now in the close-out phase. Planned 1-year clinical follow-up was available in 487 patients.

Patients in ACCESS-EU had a mean age of 73.7 years, 63.8% male, and a history of CHF (70.1%), coronary artery disease (62.7%), atrial fibrillation (67.7%) and hypertension (76.1%). 84.9% were NYHA III/IV, and the mean LVEF was 35%. Cardiac operative risk was evaluated using the EuroScore, a method more commonly used outside the US for assessing risk. The mean logistic EuroScore was 23.0% and 44.6% of patients had a logistic EuroScore of 20% or greater.

<p>Despite the broad indication for the MitraClip in Europe, the patients treated in the ACCESS-EU study were representative of the higher end of the surgical risk spectrum.</p>
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Patients enrolled in ACCESS-EU represent a population with significant, symptomatic MR, a high rate of multiple serious comorbidities. Considering the high MitraClip device implant rate (99.6%, 565/567), the high rate of meaningful MR reduction (78.9%, 258/327 MR<2+), and the resulting improvements in 6-minute walk (59.5 m difference, $p<0.0001$), Minnesota Living with Heart Failure Questionnaire quality of life score (13.5 point improvement, $p<0.0001$) and NYHA Functional Class (71.5% NYHA Class I or II, $p<0.0001$), at 1 year, it is concluded that the MitraClip device provides an important therapeutic option for patients with significant mitral regurgitation, and is an especially important option for patients who may be considered high surgical risk.

Phase II of ACCESS-EU, with the objective of collecting additional clinical data, specifically Echocardiography Core Laboratory evaluation of MR severity and other echocardiographic measures, which enrolled 286 patients, is now in the close-out phase.

5.2.7 Additional Clinical Trials

Concurrent with pursuit of MitraClip approval in the US, Abbott Vascular is sponsoring two clinical trials to further study the device in heart failure patients.

In the US, the COAPT Trial (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Extremely High Surgical Risk Patients) is a randomized pivotal trial of the MitraClip in heart failure patients with mild to moderate LV dysfunction that have FMR of severity 3+ or 4+ (MR $\geq 3+$ of degenerative etiology is excluded), who are extremely high risk for open mitral valve surgery. Eligible patients will be randomized in a 1:1 ratio to the MitraClip device (Device group) or to no MitraClip device (Control group). The primary safety endpoint of the trial is a composite of death (all-cause), stroke, worsening kidney dysfunction, permanent left ventricular assist device (LVAD) implant, or heart transplant at 12 months and the primary effectiveness endpoint is recurrent heart failure hospitalizations. The COAPT Trial is intended for advancement of the therapy and improvement of clinical understanding of the benefits of the technology in patients with heart failure. The trial will also generate health economic data and support establishment of treatment guidelines for the MitraClip therapy. The trial will enroll up to 150 roll-in and 420 patients randomized patients.

In Europe, the RESHAPE-HF Trial (a RandomizEd Study of tHe MitraCliP DEvice in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation) is a randomized trial of the MitraClip in advanced heart failure patients with severe LV dysfunction (EF 15%-40% and LVIDd ≥ 55 cm) that have FMR of severity 3+ or 4+ (MR $\geq 3+$ of degenerative etiology is excluded). Eligible patients will be randomized in a 1:1 ratio to optimal standard of care therapy and the MitraClip device (Device group) or to optimal standard of care therapy alone (Control group). The primary endpoint of the trial is a hierarchical composite of all-cause mortality and recurrent heart failure hospitalizations. The RESHAPE-HF Trial is intended to improve clinical understanding of the benefits of the technology in patients with advanced heart failure. The trial will also generate health economic data and support establishment of treatment guidelines for this new therapy. The trial will enroll approximately 800 patients.

5.2.8 Summary of Clinical Experience

A summary of the US clinical studies, including key inclusion and exclusion criteria, study endpoints, number of study sites and study patients, and identity of the study core laboratories is provided in Table 6.

The EVEREST II RCT met safety and effectiveness endpoints. However, after significant discussion with the FDA and consultation with physician advisors, and based upon the realization that the EVEREST II RCT results would not support diversion of surgical candidates to the less invasive alternative, Abbott Vascular decided to narrow the proposed indication for the MitraClip to patients too high risk for mitral valve surgery. This patient population has an unmet clinical need for a treatment option in that there is no approved medical therapy for MR reduction and these patients are not candidates for mitral valve surgery. The PMA was amended on April 22, 2011 seeking the indication in high surgical risk patients and providing an analysis of the integrated data of 211 patients from the EVEREST II HRR (n=78) and the REALISM HR studies (n=133) to demonstrate the safety and effectiveness of the MitraClip in high surgical risk patients. The PMA was further amended on August 27, 2012 to include an additional 140 REALISM High Risk patients for a total of 351 patients (n=78 EVEREST II HRR, n=273 REALISM HR) with follow-up through 1 year for an Integrated High Surgical Risk Cohort (Integrated HSR Cohort). Results from the integrated analysis are used to support the requested indication in patients too high risk to undergo open surgery.

Table 6: Overview of MitraClip US Clinical Trials (2003-Ongoing)

Study	Key Inclusion Criteria	Key Exclusion Criteria	Endpoint	CEC	ECL	# sites	# patients
EVEREST I ^a (2003-2011)	<ul style="list-style-type: none"> MR≥3+ Symptomatic or asymptomatic with^b: LVEF 30-50% and/or LVESD 50-55mm or LVEF 50-60% and LVESD < 45 mm or LVEF>60 and LVESD 45-55 mm Candidate for mitral valve surgery including cardiopulmonary bypass 	<ul style="list-style-type: none"> LVEF<30%, and/or LVESD >55mm Mitral valve orifice area <4.0 cm² Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR 	<ul style="list-style-type: none"> Primary: Major Adverse Event rate through 30 days 	HCRI	UCSF, MedStar ^a	11	55
EVEREST II RCT (including Roll-ins) (2005- Follow-up ongoing)	<ul style="list-style-type: none"> MR≥3+ 1. Symptomatic with LVEF > 25% and LVESD ≤ 55 mm or 2. asymptomatic with^b: LVEF 25% to 60% LVESD ≥ 40 mm New onset of atrial fibrillation PASP>50mmHg at rest of >60 mmHg with exercise 	<ul style="list-style-type: none"> LVEF≤25%, and/or LVESD >55mm Mitral valve orifice area <4.0 cm² Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR 	<ul style="list-style-type: none"> Primary Safety: Major Adverse Event rate through 30 days or discharge, whichever is greater Primary Effectiveness: Freedom from death, MV surgery (for Device group) or re-operation (for Control group), and MR > 2+ at 1 year Secondary Effectiveness: Measures of LV Function SF-36 quality of life NYHA Functional Class 	HCRI	UCSF, MedStar ^a	37	184 device 95 surgery 60 roll-in
EVEREST II High Risk Registry Study (2007- Follow-up ongoing)	<ul style="list-style-type: none"> MR≥3+ Predicted procedural mortality risk calculated using the STS score surgical risk calculator of ≥ 12% or in the judgment of a cardiac surgeon the patient is considered a high risk surgical candidate due to the presence of one of the following indications: <ul style="list-style-type: none"> 1. Porcelain aorta or mobile ascending aortic atheroma 2. Post-radiation mediastinum 3. Previous mediastinitis 4. Functional MR with EF<40 5. Over 75 years old with EF<40 6. Re-operation with patent grafts 7. Two or more prior chest surgeries 8. Hepatic cirrhosis 9. Three (3) or more of the following STS score high risk factors <ul style="list-style-type: none"> 9.1 Creatinine > 2.5 mg/dL 9.2 Prior chest surgery 9.3 Age over 75 9.4 EF<35 	<ul style="list-style-type: none"> LVEF<20% and/or LVESD>60mm Mitral valve orifice area <4.0 cm² Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR 	<ul style="list-style-type: none"> Primary Safety: Procedural mortality at 30 days Major Secondary: Measures of LV Function SF-36 quality of life NYHA Functional Class CHF Hospitalizations Secondary Safety: Major Adverse Event rate at 30 days and 1 year 	HCRI	UCSF, MedStar ^a	25	78

Study	Key Inclusion Criteria	Key Exclusion Criteria	Endpoint	CEC	ECL	# sites	# patients
Continued Access HR (REALISM HR) (2009-Ongoing)	<ul style="list-style-type: none"> MR≥3+ Predicted procedural mortality risk calculated using the STS score surgical risk calculator of ≥ 12% or in the judgment of a cardiac surgeon the patient is considered a high risk surgical candidate due to the presence of one of the following indications: <ol style="list-style-type: none"> 1. Porcelain aorta or mobile ascending aortic atheroma 2. Post-radiation mediastinum 3. Previous mediastinitis 4. Functional MR with EF<40 5. Over 75 years old with EF<40 6. Re-operation with patent grafts 7. Two or more prior chest surgeries 8. Hepatic cirrhosis 9. Three (3) or more of the following STS score high risk factors <ol style="list-style-type: none"> 9.1 Creatinine > 2.5 mg/dL 9.2 Prior chest surgery 9.3 Age over 75 9.4 EF<35 	<ul style="list-style-type: none"> LVEF<20% and/or LVESD>60mm Mitral valve orifice area <4.0 cm² Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR 	<ul style="list-style-type: none"> Primary Safety: Procedural mortality at 30 days Major Secondary: <ul style="list-style-type: none"> Measures of LV Function SF-36 quality of life NYHA Functional Class CHF Hospitalizations Secondary Safety: <ul style="list-style-type: none"> Major Adverse Event rate at 30 days and 1 year 	NAM SA	UCSF, MedStar ^a	39	273
Continued Access Non-HR (REALISM nHR) (2009-Follow-up ongoing)	<ul style="list-style-type: none"> MR≥3+ Symptomatic with LVEF > 25% and LVESD ≤ 55 mm or asymptomatic with^b: <ul style="list-style-type: none"> LVEF 25% to 60% LVESD ≥ 40 mm New onset of atrial fibrillation PASP>50mmHg at rest of >60 mmHg with exercise 	<ul style="list-style-type: none"> LVEF≤25%, and/or LVESD >55mm Mitral valve orifice area <4.0 cm² Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR 	<ul style="list-style-type: none"> Primary Safety: Major Adverse Event rate through 30 days or discharge, whichever is greater Primary Effectiveness: Freedom from death, MV surgery (for Device group) or re-operation (for Control group), and MR > 2+ at 1 year Secondary Effectiveness: <ul style="list-style-type: none"> Measures of LV Function SF-36 quality of life NYHA Functional Class 6 Minute Walk Test (6MWT) Distance^c 	NAMS A	UCSF, MedStar ^a	39	272

^a UCSF assessed baseline and 12-month echocardiograms for the EVEREST II RCT and High Risk Study studies; All other echocardiograms were assessed by either UCSF or MedStar.

^b Inclusion criteria based on the current indication for mitral valve surgery for mitral regurgitation in the ACC/AHA guidelines for management of valvular dysfunction.

^c In protocol version dated November 17, 2008, only patients with NYHA Functional Class III or IV in the Non-High Risk arm were considered for a 6-minute walk test. In the amended protocol version dated September 14, 2010, all patients enrolled in Continued Access are required to perform the 6-minute walk test.

6.0 Unmet Medical Need in Mitral Valve Regurgitation

With at least 250,000 patients diagnosed with clinically significant MR (symptomatic with MR severity of 3+ or 4+) each year, mitral regurgitation (MR) is the most common type of heart valve disease in the United States⁹. Patients with MR are at risk of poor quality of life, marked limitation in activity, repeated heart failure hospitalizations, and increased mortality rates. Onset of MR initially leads to impaired hemodynamics, which subsequently results in left ventricular remodeling, which in turn causes worsening MR. Thus a self-perpetuating cycle of MR is initiated. Although mitral valve repair or replacement surgery is currently standard of care, some patients with clinically significant MR are at an unacceptable risk of morbidity and mortality, and are therefore not offered surgery.^{4,5,16,18,20}

Patients who are judged at high risk for surgical complications because of underlying conditions are less likely to be referred to surgery or likely to have a surgeon decline to perform surgery due to their risk status. Medical management of clinically significant MR, such as beta blockers and ACE inhibitors, may reduce symptoms by improving fluid build-up and blood pressure³, but medical management fails to achieve mechanical reduction of mitral regurgitation¹. These individuals experience progression of heart failure and often receive only palliative care until they progress to death.

Given the significant extent of illness and the debilitating effect on quality of life for patients with clinically significant MR and the lack of effectiveness of medical management, there is a significant unmet clinical need for effective valve repair or replacement procedures that have reduced morbidity and mortality compared to surgery. The MitraClip therapy offers a percutaneous option for patients with significant morbidity and mortality risk from mitral valve surgery. Through minimally invasive mechanical reduction of MR, the MitraClip therapy addresses a significant unmet clinical need for symptomatic patients facing concurrent challenges of multiple serious comorbidities, including advanced age, compromised ejection fraction, prior cardiac surgery, renal disease, atrial fibrillation and chronic obstructive pulmonary disease (COPD).

7.0 EVEREST II High Risk Registry

7.1 EVEREST II HRR Study Design

The EVEREST II High Risk Registry (EVEREST II HRR) was a prospective, single-arm study conducted in North America to gather clinical data on the safety and effectiveness of the MitraClip in 78 patients too high risk for open mitral valve surgery with clinically significant MR (3+ or 4+), who met mitral valve anatomic criteria for the MitraClip Device (see Appendix B). Patients enrolling in the study had to have a surgical mortality risk prediction of at least 12% based on either one of the following:

- (1) Society of Thoracic Surgeons (STS) mortality risk of at least 12%.[†] In this case, the STS mortality risk was used as the surgical mortality risk prediction.
- (2) Assigned a surgical mortality risk prediction of at least 12% by a cardiac surgeon based on the presence of one or more of pre-specified surgical risk factors listed in Appendix D.

Patients were excluded from the study for severe left ventricular dysfunction. The complete list of inclusion and exclusion criteria for this study is provided in Appendix E.

Patients who met eligibility criteria for the study and underwent a MitraClip procedure, whether a MitraClip Device was implanted or not, were considered enrolled in the study. Patients are followed at discharge, 30 days, 6, 12, 18 and 24 months, and every year thereafter for 5 years, unless they withdraw consent to participate in the study. Three-year follow-up data have been submitted in the PMA. An independent Echocardiography Core Laboratory (ECL) evaluates baseline and follow-up echocardiograms. A Clinical Events Committee (CEC) adjudicated safety endpoints for the study. MR severity at baseline and follow-up in both studies was assessed based upon American Society of Echocardiography guidelines (see Appendix A).

[†] Based on a query of the STS database (2008-2012), of patients undergoing isolated mitral valve surgery, only 5.6% of patients have STS mortality risk \geq 12%.

7.1.1 EVEREST II HRR Primary Safety Endpoint

The primary safety endpoint was procedural mortality, defined as all-cause mortality at 30 days or discharge post-MitraClip procedure, whichever is longer. This endpoint was designed to demonstrate that procedural mortality post-MitraClip in patients deemed too high risk for surgery is lower than that predicted from surgery. For statistical analysis the observed procedural mortality rate was compared to the average predicted surgical mortality risk. The hypothesis was:

$$H_0: \pi_{\text{Clip}} \geq \text{Average predicted surgical mortality risk}$$

vs.

$$H_A: \pi_{\text{Clip}} < \text{Average predicted surgical mortality risk}$$

where the average predicted surgical mortality risk was a performance goal to be determined based on patients enrolled (i.e., STS mortality risk if $\geq 12\%$ or surgeon assigned mortality risk if STS mortality risk $< 12\%$), and π_{Clip} is the procedural mortality rate from treatment with the MitraClip Device in patients too high risk for surgery. The hypothesis was tested by comparing the upper bound of the 95% confidence interval for the procedural mortality rate to the average predicted surgical mortality risk for enrolled patients.

The sample size for this hypothesis assumed an 11 percentage point difference between the procedural mortality rate in the EVEREST II HRR and the predicted surgical mortality risk. Under this assumption, a sample size of 70 patients would provide 90% power at the 1-sided significance level of 0.05 to reject the null hypothesis.

Sensitivity analyses were performed to assess the effect of surgeon assessed mortality on the primary safety endpoint. The following two sensitivity analyses were carried out:

Predicted Surgical Mortality = STS Mortality Risk:

In the most conservative analysis, predicted surgical mortality was assigned as the STS mortality risk for ALL patients regardless of route of entry.

7.1.2 EVEREST II HRR Secondary Safety Endpoints

Secondary safety endpoints were descriptive in nature, and included major adverse events, major vascular complications, major bleeding complications, non-cerebral thromboembolism, endocarditis, hemolysis, thrombosis, dysrhythmias (defined as new onset of atrial fibrillation and heart block requiring placement of a permanent pacemaker), and clinically significant atrial septal defect. These events are summarized and reported as proportions on a per-patient basis at 30 days and 1 year. These endpoints were identical to

those defined in the EVEREST II RCT. In particular, the composite major adverse event endpoint in the EVEREST II RCT, which included adverse events associated with surgery (such as deep wound infection, new onset of permanent atrial fibrillation), was left unchanged in the EVEREST II HRR. These endpoints were adjudicated by an independent Clinical Events Committee (CEC) through 1 year. Definitions of these endpoints are provided in Appendix C.

Safety endpoints were summarized as the proportion of patients with the event and there is no hierarchical ranking of the components. 30-day events include events that occurred through 30 days or discharge, whichever is longer.

7.1.3 EVEREST II HRR Mortality Comparators

It was important to put mortality rates in this single-arm study in perspective. The following list of comparators was utilized.

Surgical Comparator for Mortality:

As the EVEREST II HRR was a single-arm study, procedural mortality was compared to the predicted surgical mortality in these patients. The predicted surgical mortality was the STS mortality risk (if STS mortality risk $\geq 12\%$) or surgeon assessed mortality risk (if the patient had other high surgical risk factors). This was the primary endpoint of the study.

Concurrent Control (Standard of Care) Comparator for Mortality:

Upon completion of enrollment in the EVEREST II HRR, a retrospective comparator for freedom from death at 1 year was defined to consist of patients with MR 3+/4+ who were screened for the EVEREST II HRR and were too high risk for surgery but did not enroll (“Concurrent Control”).

A total of 84 patients with MR 3+/4+ who were screened for the EVEREST II HRR but did not enroll were available. Thirty-six (36) patients make up the Concurrent Control group on whom baseline characteristics, surgical status and mortality data were retrospectively collected from either the patient or the patient’s family. Among the remaining 48 patients, 26 did not meet the protocol criteria for high surgical risk, 11 were excluded due to lack of IRB approval to retrospectively gather data, 5 were excluded due to lack of informed consent (from patient or patient’s family) and 6 patients and/or their families were unable to be contacted.

Table 7 summarizes the reasons why the 36 patients comprising the Concurrent Control were not enrolled in the EVEREST II HRR. A majority (58.3%) were excluded from the study

due to not meeting mitral valve anatomy eligibility for the MitraClip. Therefore, there is inherent bias in the composition of the Concurrent Control, as many patients were not eligible to be treated with the MitraClip Device.

Table 7: Reason Concurrent Control Patients Not Enrolled in EVEREST II HRR

Reason Not Enrolled	Number of Patients (N = 36)
Approved, Not Treated (Refused consent or enrollment in EVEREST II HRR complete)	8 (22.2%)
Transthoracic echocardiogram pending or contraindicated/ MV anatomy unknown	7 (19.4%)
Excluded for not meeting mitral valve anatomy eligibility for MitraClip	21 (58.3%)

Literature comparators also were considered to put the EVEREST II HRR mortality in perspective. A literature search was undertaken to review 30-day and 1-year mortality rates in patient populations similar to the EVEREST II HRR. The search was carried out using MEDLINE (PUBMED) for all English-only journals published during the period between 1997 and 2010. As patient-level data are not reported, an exact match to the MitraClip patient population was not found because specific definitions regarding MR severity were not reported and baseline risks varied widely. Therefore, any conclusions that can be drawn from literature comparators are limited.

7.1.4 EVEREST II HRR Major Effectiveness Endpoints

Clinical benefits with medical management for MR are limited as they provide symptom management but do not fix the leaky valve. Without mechanical correction of MR, patients are expected to experience left ventricular remodeling, worsening heart failure and poor quality of life. The following clinical measures of benefit, which were specified in the EVEREST II HRR, were consistent with the EVEREST II RCT:

- Measures of left ventricular size, as assessed by the ECL, were tested in the following order to preserve type I error at the 0.05 significance level:
 - Left ventricular end diastolic volume (LVEDV):
 $H_0: \mu_{LVEDV \text{ Baseline}} = \mu_{LVEDV \text{ 1 year}}$ and $H_A: \mu_{LVEDV \text{ Baseline}} > \mu_{LVEDV \text{ 1 year}}$
 - Left ventricular internal diameter, diastole (LVIDd):
 $H_0: \mu_{LVIDd \text{ Baseline}} = \mu_{LVIDd \text{ 1 year}}$ and $H_A: \mu_{LVIDd \text{ Baseline}} > \mu_{LVIDd \text{ 1 year}}$
 - Left ventricular end systolic volume (LVESV):
 $H_0: \mu_{LVESV \text{ Baseline}} = \mu_{LVESV \text{ 1 year}}$ and $H_A: \mu_{LVESV \text{ Baseline}} > \mu_{LVESV \text{ 1 year}}$
 - Left ventricular end systolic dimension (LVIDs):
 $H_0: \mu_{LVIDs \text{ Baseline}} = \mu_{LVIDs \text{ 1 year}}$ and $H_A: \mu_{LVIDs \text{ Baseline}} > \mu_{LVIDs \text{ 1 year}}$

Paired t-tests with a 1-sided significance level of 0.05 were used to assess whether the improvement from baseline to 1 year was statistically significant.

- Descriptive endpoints:
 - NYHA Class
 - SF-36 Quality of Life score
 - Hospitalizations for heart failure (not an endpoint in the EVEREST II RCT)

The proportion of patients in NYHA Class III or IV and physical and mental component summary scores for the SF-36 QoL questionnaire at 1 year versus baseline are summarized for patients with data available at both timepoints (mean, SD, Table 12). P-values comparing the mean change from baseline to 1 year are presented for descriptive purposes. Hospitalizations for heart failure are summarized as annualized rates for the year prior to undergoing the MitraClip procedure and the year post-discharge from the MitraClip procedure using a Poisson regression model with an offset for the length of follow-up (Appendix E, Table 76). The hospitalization rates from this model were statistically significant between timepoints, with fewer annualized rates of hospitalization the year following discharge after MitraClip implantation.

7.1.5 EVEREST II HRR Comparators for Effectiveness

Since the EVEREST II HRR was a single arm study, measures of clinical benefit were analyzed as improvement from baseline, using patients as their own control. Clinical benefits with medical management for MR are limited as they provide some symptom management but do not repair the leaky valve.

7.2 EVEREST II HRR Results

7.2.1 EVEREST II HRR Baseline Demographic Characteristics and Medical History

Seventy-eight (78) patients were enrolled in the EVEREST II HRR. Table 8 lists the baseline demographic characteristics and medical history comparing the EVEREST II HRR and Concurrent Control. Patients enrolled in the EVEREST II HRR were elderly and more co-morbid at baseline than patients enrolled concurrently in the EVEREST II RCT (Table 8). The average predicted surgical mortality for the EVEREST II HRR was 18.2%. The study enrolled patients of both degenerative and functional MR etiologies (41% DMR, 59% FMR). Key baseline demographics and co-morbidities were similar between the EVEREST II HRR and Concurrent Control groups.

Table 8: EVEREST II HRR - Baseline Demographic Characteristics and Medical History

Characteristic % (n/N)	EVEREST II HRR (N = 78)	Concurrent Control (N = 36)	p-value ^a
Age (years), Mean ± SD (N)	76.7 ± 9.8 (78)	77.2 ± 13.0 (36)	0.854
Patients over 75 years of age	61.5% (48/78)	63.9% (23/36)	0.839
Female Gender	37.2% (29/78)	50.0% (18/36)	0.223
Coronary Artery Disease	84.2% (64/76)	71.4% (25/35)	0.131
Prior Myocardial Infarction	55.8% (43/77)	36.4% (12/33)	0.010
Atrial Fibrillation History	61.6% (45/73)	52.8% (19/36)	0.413
Prior Stroke	10.3% (8/78)	13.9% (5/36)	0.545
Diabetes	41.0% (32/78)	41.7% (15/36)	>0.99
Moderate to Severe Renal Disease	23.1% (18/78)	31.4% (11/35)	0.360
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O ₂)	34.6% (27/78)	30.6% (11/36)	0.831
Previous Cardiovascular Surgery	59.0% (46/78)	50.0% (18/36)	0.420
Previous Percutaneous Coronary Intervention	38.5% (30/78)	30.6% (11/36)	0.530
NYHA Class III/IV Heart Failure	89.7% (70/78)	83.9% (26/31)	0.513
Functional MR Etiology	59.0% (46/78)	63.9% (23/36)	0.128
LV Ejection Fraction (%), Mean ± SD (N)	54.4 ± 13.7 (78)	55.2 ± 18.1 (35)	0.815
LV Internal Diameter systole (cm), Mean ± SD (N)	3.9 ± 1.1 (78)	3.8 ± 1.1 (36)	0.458
Predicted Surgical Mortality Risk (%), Mean ± SD (N)	18.2 ± 8.0(78)	17.4 ± 7.4	0.418

^a Two-sample t-test or Fisher's exact test, as appropriate

7.2.2 EVEREST II HRR Safety Results

7.2.2.1 EVEREST II HRR Intra-Procedural Events

No intra-procedural deaths were observed. Intra-procedural events were rare, with no immediate conversions to surgery (Table 9). Only one case of tamponade occurred during the transseptal procedure, resulting in the MitraClip procedure being aborted. No MitraClip Devices embolized during the procedure.

Table 9: EVEREST II HRR – Intra-Procedural Events

Event	% (n/N)
Intra-Procedural Death	0.0% (0/78)
Immediate Surgical Conversion	0.0% (0/78)
Tamponade during transseptal procedure	1.3% (1/78)
MitraClip Embolization	0.0% (0/78)

7.2.2.2 EVEREST II HRR Post-Procedural Events

The mean post-procedure ICU/CCU/PACU stay was 2.2 days and the mean hospital stay was 3.9 days with a median of 2 days (Table 10). Approximately 75% of patients were discharged home without the need for professional home healthcare. An additional 10 % were discharged home with home healthcare required, resulting in a total of almost 86% being discharged home after the MitraClip procedure.

Table 10: EVEREST II HRR – Post-Procedural Results

Post-Procedural Characteristic	EVEREST II HRR (N = 78)
Post-Procedure ICU/CCU/PACU Duration (days)	
Mean ± SD	2.2 ± 3.4 (78)
Median	1.1
Post-Procedure Hospital Stay (days)	
Mean ± SD	3.9 ± 6.4 (78)
Median	2
Discharge Status	
Home without home healthcare	75.6% (59/78)
Home healthcare required	10.3% (8/78)
Skilled nursing/Long-term acute care	10.3% (8/78)
Death	3.8% (3/78)

7.2.2.3 EVEREST II HRR Primary Safety Endpoint Results

EVEREST II HRR Procedural Mortality vs. Predicted Surgical Mortality:

Six (7.7%) of 78 patients in the EVEREST II HRR died within 30 days or discharge, whichever was longer (Table 11). The upper confidence bound for procedural mortality (14.8%) was lower than the predicted surgical mortality (STS or surgeon assessed, $p = .006$). Additionally, in the sensitivity analysis using the STS risk as the predicted surgical mortality, the observed mortality rate was lower than the average STS risk, however, this did not reach statistical significance ($p = 0.057$).

Table 11: EVEREST II HRR – Primary Safety Endpoint

	EVEREST II HRR (N = 78)
Observed Procedural Mortality	7.7% (6/78)
95.472% Upper Confidence Bound (UCB) ^a	14.8%
Average Predicted Surgical Mortality (STS or Surgeon Assessed)	18.2% ($p = 0.006$)
Average Predicted Surgical Mortality (STS Mortality Risk)	14.2% ($p = 0.057$)

^a UCB is based on the Clopper-Pearson method and confidence level is adjusted for an interim analysis
p-values obtained by Monte-Carlo simulations

EVEREST II HRR Procedural Mortality vs. Concurrent Control Comparator:

The 30-day mortality rate in the Concurrent Control was 8.3%. The difference in 30-day mortality between the EVEREST II HRR and Concurrent Control is not statistically significant ($p > 0.99$). However, as there is inherent bias in the composition of the Concurrent Control, results are difficult to interpret and no conclusions are able to be drawn from this comparator.

7.2.2.4 EVEREST II HRR Secondary Safety Endpoint Results

Secondary safety endpoint results are summarized in Appendix E. Stroke, myocardial infarction and prolonged ventilation (> 48 hours) each occurred at a rate of 2.6% and renal failure occurred at a rate of 3.8% at 30 days (Appendix E, Table 73). There was no incidence of non-elective (urgent/emergent) cardiovascular surgery for adverse events or new onset of persistent atrial fibrillation in this cohort through 1 year. Major vascular complications occurred at a relatively low rate of 2.6% at 30 days given that access to the mitral valve is achieved via the femoral vein and inferior vena cava (Appendix E, Table 74). Major bleeding complications occurred at a rate of 16.7% at 30 days and clinically significant atrial septal defect requiring treatment occurred at a rate of 2.6%. These adverse event rates are not unexpected for this elderly, highly co-morbid population.

Kaplan-Meier freedom from mortality at 1 year in the EVEREST II HRR was 75.4%. In comparison, the freedom from mortality in the Concurrent Control was 55.3%. While this difference was statistically significant ($p = 0.047$), there is inherent bias in the composition of the Concurrent Control, therefore, no conclusions are able to be drawn from this comparator.

7.2.3 EVEREST II HRR Effectiveness Results**7.2.3.1 EVEREST II HRR Implant Success**

Implant success in the EVEREST II HRR was high with 96.2% of patients implanted with one (59.0%) or two (37.2%) MitraClip devices (see Section 9.2, Table 60).

7.2.3.2 EVEREST II HRR Hemodynamic Results

Acute hemodynamic measurements obtained during the index procedure just prior to device deployment, and 10 minutes post-device deployment while under general anesthesia, are summarized in Table 12. Implanting the MitraClip results in hemodynamic improvements as expected.

Table 12: EVEREST II HRR - Hemodynamic Results
Patients with Paired Data

Hemodynamic Variable	N	Pre-procedure Mean \pm SD	10 Minutes Post-device deployment Mean \pm SD	p-value
Cardiac Output, L/min	74	4.6 \pm 2.1	5.6 \pm 2.7	0.001
Pulmonary Capillary Wedge Pressure V wave, mmHg	58	26 \pm 15	21.3 \pm 9.6	0.023
Systemic Arterial Pressure (Systolic), mmHg	75	109.3 \pm 21.1	113.5 \pm 19.3	0.087

7.2.3.3 EVEREST II HRR Major Effectiveness Endpoint Results

Left ventricular measurements at baseline and 1 year in patients with ECL assessed measurements at both time points are summarized in Table 13. The table demonstrates reduction in all four pre-specified parameters of left ventricular size, however, the reduction in LVIDs did not achieve statistical significance. It is concluded that LVEDV, LVIDd and LVESV are significantly reduced at 1 year following the MitraClip procedure. These reductions are indicative of left ventricular reverse remodeling associated with MR reduction.

Table 13: EVEREST II HRR – Left Ventricular Size at Baseline and 1 Year
Patients with Paired Data at Baseline and 1 Year

LV Measurement	N	Baseline	1 Year	Difference (1-Year- Baseline)	p-value
LVEDV, ml					
Mean \pm SD	54	171.8 \pm 50.5	139.7 \pm 42.6	-32.1 \pm 28.1	<0.0001
97.5% Upper Conf Bound				-24.4	
LVIDd, cm					
Mean \pm SD	54	5.6 \pm 0.7	5.3 \pm 0.7	-0.3 \pm 0.4	<0.0001
97.5% Upper Conf Bound				-0.2	
LVESV, ml					
Mean \pm SD	54	82.2 \pm 42.1	72.2 \pm 35.8	-10.0 \pm 21.5	0.0006
97.5% Upper Conf Bound				-4.1	
LVIDs cm					
Mean \pm SD	54	3.9 \pm 1.1	3.8 \pm 1.0	-0.1 \pm 0.6	0.0913
97.5% Upper Conf Bound				0.1	

Refer to Appendix E for results on MR reduction, NYHA Class, SF-36 quality of life scores and heart failure hospitalizations.

7.2.4 EVEREST II HRR Conclusions

The EVEREST II HRR met its safety and effectiveness endpoints. Observed procedural mortality with the MitraClip was lower than predicted surgical mortality. Adverse events occurred at rates as expected in an advanced age patient population with significant co-morbidities. LVEDV, LVIDd and LVESV were significantly reduced at 1 year following the MitraClip procedure. Patients experienced meaningful improvements in NYHA Class, quality of life and rate of heart failure hospitalizations at 1 year. These improvements are consistent with a clinically meaningful reduction in MR accompanied by reverse left ventricular remodeling. The magnitudes of the changes were as expected; lower than those observed in the RCT surgical Control group, and similar to those observed in the RCT MitraClip group.

8.0 Integrated Analysis of High Surgical Risk Cohort

8.1 Overview of REALISM Continued Access High Risk Arm

The REALISM HR study is a US continued access study enrolling patients deemed too high risk for surgery. As of January 2013, 583 high surgical risk patients have been enrolled in REALISM HR, with 1-year follow-up data available on 273 patients. The study was designed to collect valuable new information regarding use of the MitraClip System under more “real world” conditions in addition to providing additional safety and effectiveness data in support of the pre-market approval application (PMA). Eligibility criteria in REALISM HR are identical to EVEREST II HRR, with one exception: patients are excluded from REALISM HR if they had a concurrent medical condition resulting in a life expectancy of less than 1 year. This criterion was added to exclude terminally ill patients, including those in hospice. Safety, effectiveness and follow-up data collection in the REALISM HR protocol are identical to EVEREST II HRR, with enrollment and follow-up ongoing through 5 years. An independent CEC adjudicates major adverse events through 1 year. An independent Echocardiography Core Laboratory evaluates baseline and follow-up echocardiograms. Safety and effectiveness data for the REALISM HR study are included in Appendix F.

8.2 Justification for Pooling High Surgical Risk Patients from EVEREST II HRR and REALISM HR Continued Access

The REALISM study was designed to continue to collect information regarding use of the MitraClip in order to provide additional safety and effectiveness data in support of the pre-market approval application (PMA). Analyses of poolability of REALISM HR and EVEREST II HRR patients were specified in the REALISM protocol. The evaluation of poolability of patient data from the EVEREST II HRR and REALISM HR studies is justified because no changes in critical engineering, eligibility criteria or clinical study conduct were made between the two studies.

Baseline characteristics listed in Table 14 were pre-specified in the REALISM protocol for the evaluation of poolability of the EVEREST II HRR with REALISM HR studies. Both groups are elderly and highly co-morbid, with comparable rates of both cardiac and non-cardiac co-morbidities. Statistically significant differences were found for LVEF, LVIDs and MR etiology, with Functional MR etiology being more common in REALISM HR than EVEREST II HRR. Despite the statistical differences in LVEF and LVIDs, both studies enrolled patients with mild-to-moderate left ventricular dysfunction and specifically excluded patients with severe left ventricular dysfunction. The impact of the difference in Functional MR etiology rates between the two groups is evaluated in subgroup analyses by MR etiology.

Table 14: REALISM HR (N = 273) and EVEREST II HRR (N = 78)
Assessment of Poolability

Characteristic % (n/N)	REALISM HR (N = 273)	EVEREST II HRR (N = 78)	p-value
Age (years), Mean \pm SD (N)	75.5 \pm 10.7 (273)	76.7 \pm 9.8 (78)	0.353
Female Gender	39.6% (108/273)	37.2% (29/78)	0.793
Body Mass Index (kg/m ²), Mean \pm SD (N)	26.9 \pm 12.9 (273)	26.6 \pm 5.0 (78)	0.749
Atrial Fibrillation History	70.5% (172/244)	61.6% (45/73)	0.155
Diabetes	39.0% (106/272)	41.0% (32/78)	0.793
Myocardial Infarction	49.3% (134/272)	55.8% (43/77)	0.366
Chronic Obstructive Pulmonary Disease			0.223
With home O ₂	11.4% (31/272)	10.3% (8/78)	
Without home O ₂	15.8% (43/272)	24.4% (19/78)	
None	72.8% (198/272)	65.4% (51/78)	
Stroke	13.6% (37/273)	10.3% (8/78)	0.565
NYHA Class III/IV Heart Failure	83.5% (228/273)	89.7% (70/78)	0.211
Functional MR Etiology	73.3% (200/273)	59.0% (46/78)	0.018
Previous Cardiovascular Surgery	60.1% (164/273)	59.0% (46/78)	0.896
LV Internal Dimension, systole (cm), Mean \pm SD (N)	4.5 \pm 1.1 (245)	3.9 \pm 1.1 (78)	< 0.0001
LV Ejection Fraction, % Mean \pm SD (N)	45.2 \pm 13.6 (240)	54.4 \pm 13.7 (78)	< 0.0001

^a Sample sizes or denominators smaller than those in the header reflect missing data

8.3 Findings in the Integrated High Surgical Risk Cohort (N = 351)

Pooling of EVEREST II HRR (N = 78) and REALISM HR (N = 273) patients resulted in 351 patients deemed too high risk for open mitral valve surgery. As described in Appendix D, patients were considered high surgical risk if their STS calculated risk score was $\geq 12\%$, or if their surgeon investigator deemed that the patient was high surgical risk based on one or more pre-specified surgical risk factors as defined in the study protocol. This pooled cohort is referred to as the Integrated High Surgical Risk Cohort (Integrated HSR Cohort). The EVEREST II HRR met pre-specified endpoints. Re-analysis of these endpoints with the Integrated HSR Cohort was expected to yield greater precision in the reported estimates of the safety and effectiveness endpoints.

8.3.1 Integrated High Surgical Risk Cohort Safety Endpoints

The safety endpoints for the Integrated HSR Cohort are identical to the EVEREST II HRR. The primary safety endpoint was procedural mortality, defined as all-cause mortality at 30 days or discharge post-MitraClip procedure, whichever is longer. Secondary safety endpoints included major adverse events, major bleeding complications, non-cerebral thromboembolism, endocarditis, hemolysis, thrombosis, dysrhythmias (defined as new onset of atrial fibrillation and heart block requiring placement of a permanent pacemaker), and clinically significant atrial septal defect at 30 days and 1 year.

8.3.1.1 Integrated High Surgical Risk Cohort Comparators for Safety

The primary safety endpoint of procedural mortality was reanalyzed for the Integrated HSR Cohort. Comparisons to the literature comparators and Concurrent Control had limitations as previously discussed. FDA expressed concerns about comparing effectiveness to medical management (patient's baseline value) but safety of MitraClip to surgery. Upon request from FDA to identify alternative safety comparators, a patient level comparator for mortality (natural history of mitral regurgitation) from a single-center cardiac database (Duke University Medical Center) was identified and is described below.

Single-Center Cardiac Database Comparator:

In 2011, Abbott Vascular worked to identify databases to enable access to patient-level data on patients with diagnosis of MR $\geq 3+$. Databases at the following centers were evaluated: Ohio State University (OSU), Duke University Medical Center and Mayo Clinic.

The OSU database was identified to contain patients with a diagnosis of MR based on ICD-9 diagnosis code. However, MR severity grade was not available. Therefore, only descriptive comparisons were feasible and patient-level matching was not pursued. The Mayo Clinic database consisted of a limited number of patients with MR 3+/4+ from a single county (Olmstead County). Therefore, no comparison of survival has been performed.

The Duke University Medical Center database consisted of patient-level data with echocardiographic, medical history and follow-up data on a large number of patients with MR $\geq 3+$. This database allowed for formal comparisons of survival in patients deemed too high risk for surgery treated with the MitraClip procedure to similar patients managed non-surgically at the Duke University Medical Center despite clear Class I indications for surgery according to the ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease. A propensity matched analysis was conducted on 211 high surgical risk patients with 1 year follow-up available at the time of the analysis (October 2011)[§]. The 211 patient

[§] At the time of the Duke comparative analysis (Oct 2011), the Integrated High Surgical Risk Cohort consisted of a total of 211 patients with complete 1 year follow-up (78 EVEREST II HRR + 133 REALISM HR). All 211 patients were included in the propensity matched analysis with Duke. In parallel to conduct of the Duke Analysis, patient enrollment and follow-up in REALISM HR continued, and the Integrated High Surgical Risk Cohort was updated in August 2012 to include a total of 351 patients with 1 year follow-up (78 EVEREST II HRR + 273 REALISM HR). Thus, the 211 high surgical risk MitraClip patients used for the Duke Analysis were a subset of the 351 high surgical risk MitraClip patients in the current Integrated High Surgical Risk Cohort. To avoid confusion, the 211 MitraClip patients used for the Duke Analysis will henceforward be referred to as the "MitraClip Propensity Score Analysis Cohort" (MC PSA Cohort) and the 351 MitraClip patients will be referred to as the Integrated High Surgical Risk Cohort (Integrated HSR Cohort).

cohort (MitraClip Propensity Score Analysis Cohort or MitraClip PSA Cohort) was derived by combining 78 EVEREST II HRR patients with 133 REALISM HR patients who were enrolled between January 2009 and Feb 2010, who completed 1-year follow-up at the time of this analysis. The propensity matched analysis was independently performed by Duke University Medical Center. The Sponsor had no access to individual patient-level data and remained blinded to survival outcomes until matching was complete. A full report, including details on the matching methodology is provided in Appendix H.

The MitraClip PSA Cohort (N = 211) was expanded to include an additional 140 REALISM HR patients enrolled between Jan 2010 and March 2011, resulting in the Integrated HSR Cohort (N = 351). Results on the Integrated HSR Cohort were submitted to FDA in August 2012. In the time between the August 2012 submission and the planned Advisory Panel meeting, there has not been an opportunity to complete matching analysis for the expanded dataset to the Duke Cohort with full review by FDA. However, an unadjusted analysis of survival comparing the Integrated HSR cohort (N = 351) to the Duke Cohort is provided.

8.3.2 Integrated High Surgical Risk Cohort Effectiveness Endpoints

The effectiveness endpoints for the EVEREST II HRR were reanalyzed for the Integrated HSR Cohort, and included measures of LV size and function, SF-36 Quality of Life score, NYHA Functional Class and heart failure hospitalizations.

8.3.2.1 Integrated High Surgical Risk Cohort Comparators for Effectiveness

Comparison to Baseline (Medical Management):

Clinical benefits with medical management for MR are limited as they provide symptom management but do not fix the leaky valve. Without mechanical correction of MR, patients are expected to experience left ventricular remodeling, worsening heart failure and poor quality of life. As with the EVEREST II HRR, changes in left ventricular size, NYHA Class, quality of life and heart failure hospitalizations from baseline to 1 year were assessed for the Integrated HSR Cohort.

Surgical Comparator:

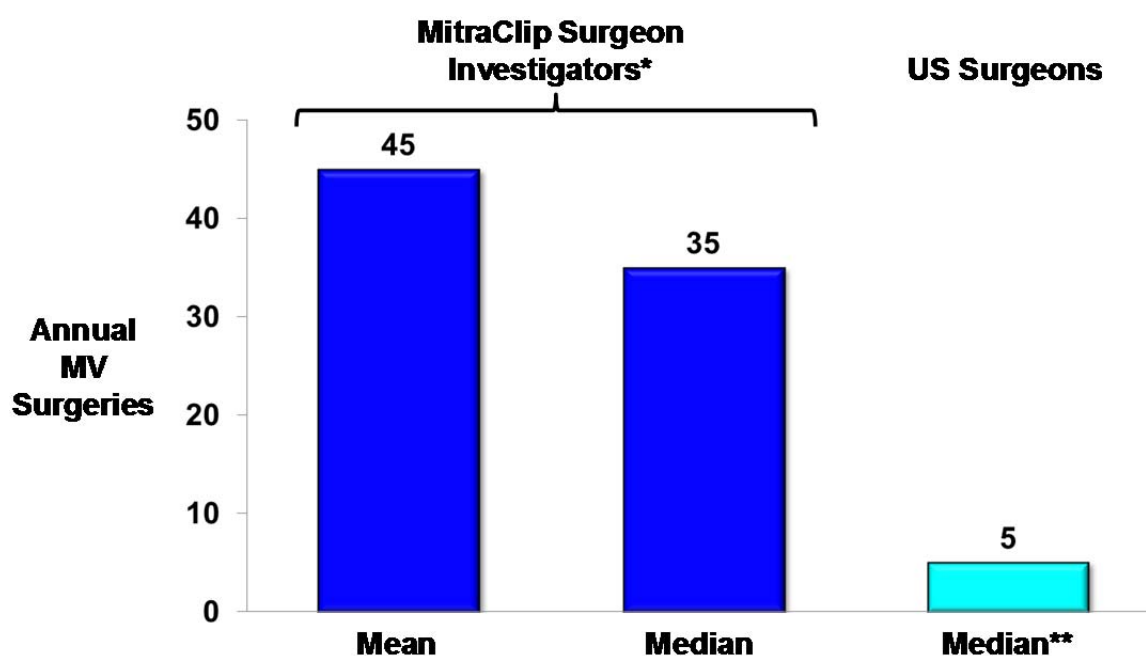
FDA expressed concerns about comparing safety (procedural mortality) of MitraClip to surgery but effectiveness to medical management (baseline). Upon request from FDA, the EVEREST II RCT surgical Control group is utilized as a contemporary comparator for effectiveness at 1 year. This is reasonable since eligibility criteria for MR etiology, valve anatomy and degree of MR severity were identical between EVEREST II RCT, EVEREST II

HRR and REALISM. Thus, consistency in measures of clinical benefit in patients treated with the MitraClip is expected, regardless of risk. These benefits are expected to be smaller than achieved with surgery as MitraClip is less effective in reducing MR.

8.3.3 Surgeon Experience

Since high risk status of patients in this cohort was determined by a cardiac surgeon, it was important to evaluate the experience of the surgeon investigators. Surgeon investigators who evaluated patients in the Integrated HSR Cohort were experienced. The median mitral valve surgeries in the year prior to patient enrollment was 35 (Figure 8). In contrast, the median US experience is 5 mitral valve surgeries.

Figure 8: Surgeon Investigator Experience



* Year prior to patient enrollment

**Bolling et al. Ann. Thorac. Surg (2010)

8.3.4 Integrated High Surgical Risk Cohort Baseline Demographic Characteristics and Medical History

Baseline demographic characteristics and medical history of the Integrated HSR Cohort are consistent with a patient population at high risk for surgery (Table 15). Compared to EVEREST II RCT patients, Integrated HSR Cohort patients had more extensive underlying

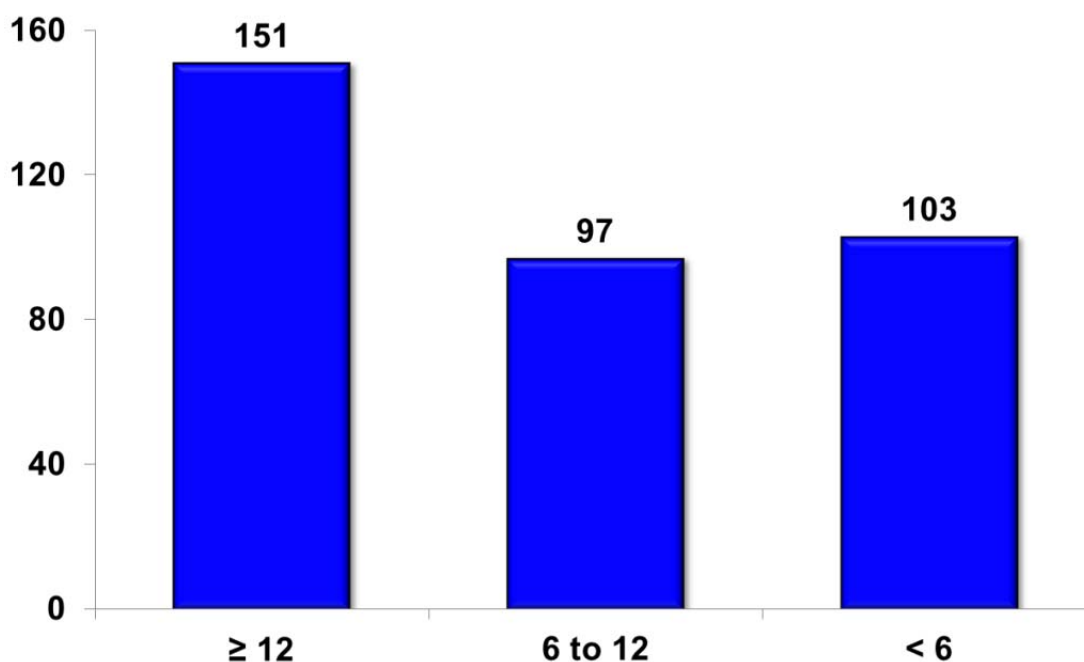
cardiovascular disease including more patients with a prior myocardial infarction and class III or IV NYHA than patients included in the EVEREST II RCT.

Table 15: Integrated HSR Cohort – Baseline and Demographic Characteristics

Characteristic	Integrated HSR Cohort (N = 351)	EVEREST II RCT (N = 279)
Age (years) Mean ± SD (N)	75.7±10.5 (351)	66.7±12.8 (279)
Patients over 75 years of age	58.1% (204/351)	29.0% (81/279)
Female Gender	39.0% (137/351)	36.2% (101/279)
Coronary Artery Disease	82.2% (287/349)	46.8% (130/278)
Prior Myocardial Infarction	50.7% (177/349)	21.7% (60/277)
Atrial Fibrillation History	68.5% (217/317)	35.6% (94/264)
Prior Stroke	12.8% (45/351)	2.2% (6/279)
Diabetes	39.4% (138/350)	8.6% (24/279)
Moderate to Severe Renal Disease	30.5% (107/351)	2.9% (8/279)
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	28.9% (101/350)	14.7% (41/278)
Hypertension	89.5% (314/351)	74.6% (208/279)
Previous Cardiovascular Surgery	59.8% (210/351)	21.1% (59/279)
Previous Percutaneous Coronary Intervention	49.9% (175/331)	21.2% (59/278)
NYHA Class III/IV Heart Failure	84.9% (298/351)	49.8% (139/279)
Functional MR Etiology	70.1% (246/351)	26.9% (75/279)
LV Ejection Fraction (%) Mean ± SD (N)	47.5 ± 14.2 (318)	60.2±10.4 (277)
LV Internal Diameter systole (cm) Mean ± SD (N)	4.4 ± 1.1 (323)	3.6±0.9 (275)

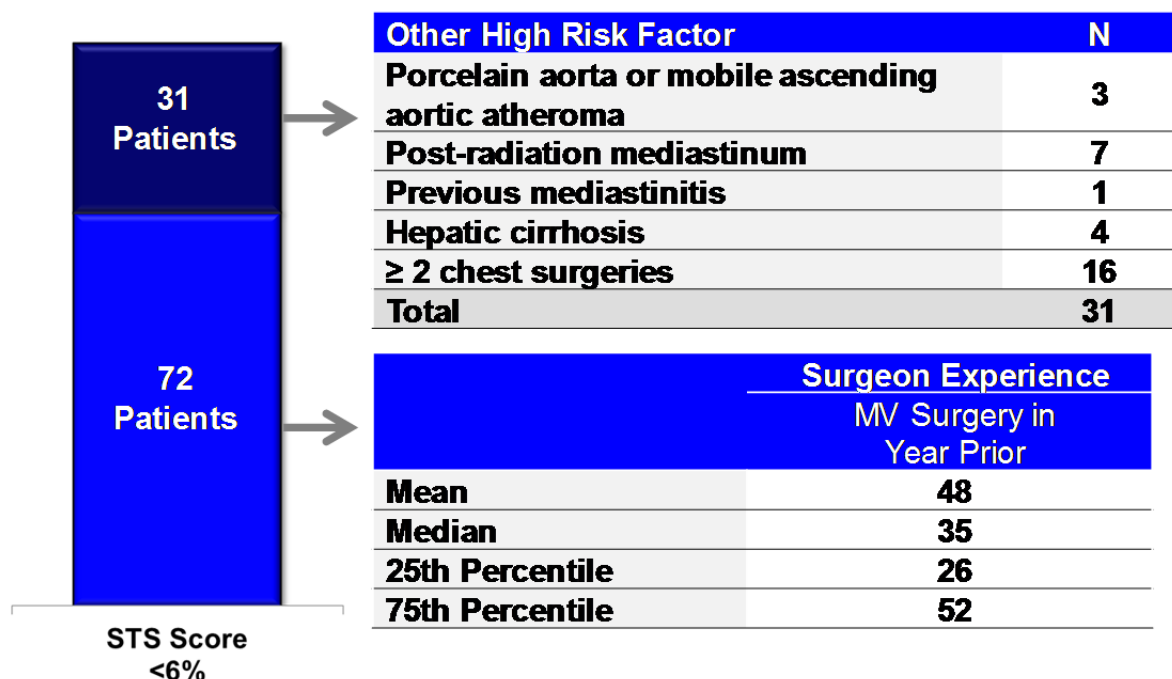
Patients were considered high surgical risk if their STS calculated risk score was $\geq 12\%$, or if their surgeon investigator deemed that the patient was high surgical risk based on one or more pre-specified surgical risk factors as defined in the study protocol. Figure 9 shows the distribution of STS mortality risk scores in the Integrated HSR Cohort. Of the 351 patients, 151 had a calculated STS mortality risk of $\geq 12\%$. Of patients who were entered based on surgeon determination of high risk, 97 had STS mortality risk between 6% and 12% and 103 had STS mortality risk less than 6%. Patients with an STS score greater than 6% comprise only 15% of the STS database (Appendix L).

Figure 9: Integrated HSR Cohort – Distribution of STS Mortality Risk



Thirty-one (31) of the 103 patients with an STS mortality risk of < 6% presented with one of 5 surgical risk factors that are well accepted as too high risk for surgery (Figure 10). These risk factors were pre-specified in the protocol and include porcelain aorta or mobile ascending aortic atheroma (3), post-radiation mediastinum (7), previous mediastinitis (1), hepatic cirrhosis (4), and two or more chest surgeries (16). The remaining 72 patients, in addition to meeting other protocol-specified surgical risk factors, had serious comorbidities contributing to a determination of high surgical risk such as cancer, AIDS, immunosuppression, and connective tissue disease. Furthermore, the surgeons who estimated the risk for these 72 patients with an STS mortality risk < 6% were highly experienced and performed, on average, 48 mitral valve surgeries in the prior year.

Figure 10: Integrated HSR Cohort – Risk Determination in Patients with STS Score < 6%



As with TAVR, medical societies will establish practice guidelines for centers to perform the MitraClip procedure, including surgeon experience. Abbott intends to work only with highly experienced surgical centers with clear labeling defining patients deemed too high risk for surgery, which will mitigate the possibility of low or medium risk patients treated post-approval.

8.3.5 Integrated High Surgical Risk Cohort Safety Results

8.3.5.1 Integrated High Surgical Risk Cohort Intra-Procedural Events

No intra-procedural deaths were observed. Intra-procedural events were rare, with no immediate conversions to surgery. Only one case of tamponade occurred during the transseptal procedure resulting in the MitraClip procedure being aborted. No MitraClip Devices embolized during the procedure.

Table 16: Integrated HSR Cohort – Intra-Procedural Events

Event	% (n/N)
Intra-Procedural Death	0.0% (0/351)
Immediate Surgical Conversion	0.0% (0/351)
Tamponade during transseptal procedure	0.3% (1/351)
MitraClip Embolization	0.0% (0/351)

8.3.5.2 Integrated High Surgical Risk Cohort Post-Procedural Results

The mean ICU stay was 1.5 days and the mean hospital stay was 3.2 days (Table 17). These are much shorter than ICU and hospital stays following mitral valve surgery. These short ICU and hospital stays are especially important in a high risk elderly population who would otherwise be hospitalized for longer durations after surgery.

Although there was no procedural mortality, the mortality rate prior to discharge was 2.6%. Almost 85% of patients were discharged home without the need for professional home healthcare. An additional 6.8% were discharged home with home healthcare, resulting in a total of almost 92% being discharged home after the MitraClip procedure and avoiding the need for a nursing home or chronic care facility.

Table 17: Integrated HSR Cohort – Post-Procedural Results

Post-Procedural Characteristic	Integrated HSR Cohort (N = 351)
Post-Procedure ICU/CCU/PACU Duration (days)	
Mean \pm SD	1.5 \pm 2.5
Median	1.0
Post-Procedure Hospital Stay (days)	
Mean \pm SD	3.2 \pm 4.9
Median	2.0
Discharge Status	
Home without home healthcare	84.9%
Home healthcare required	6.8%
Skilled nursing/Long-term acute care	5.7%
Death	2.6%

8.3.5.3 Integrated High Surgical Risk Cohort Primary Safety Endpoint Results

Integrated HSR Cohort Procedural Mortality vs. Surgical Comparator (Primary Endpoint):

Seventeen (17 or 4.8%) of 351 patients in the Integrated High Surgical Risk Cohort died within 30 days or discharge, whichever was longer (Table 18). This rate is smaller than the average predicted surgical mortality risk (18.2%).

The p-value for the comparison of observed procedural mortality to predicted surgical mortality from Monte-Carlo simulations was < 0.0001 . Sensitivity analyses were conducted to evaluate this endpoint. Specifically, the STS mortality risk was assigned as the predicted surgical mortality for all patients, including patients who were enrolled based on surgeon assessment of predicted mortality. This analysis also showed that the observed procedural mortality was lower than the predicted surgical mortality when the STS mortality risk was used for all patients ($p < 0.0001$).

Table 18: Integrated HSR Cohort – Primary Safety Endpoint

	Integrated HSR Cohort (N = 351)
Observed Procedural Mortality	4.8% (17/351)
97.5% Upper Confidence Bound (UCB) ^a	7.6%
Average Predicted Surgical Mortality (STS or Surgeon Assessed)	18.3% (p < 0.0001)
Average Predicted Surgical Mortality (STS Mortality Risk)	11.3% (p < 0.0001)
^a UCB is based on the Clopper-Pearson method	
p-values based on Monte-Carlo simulations	

These analyses were repeated for each of the following subgroups: FMR/DMR, Male/Female, and STS $\geq 12\%$ /STS < 12% (see Section 8.3.5.6). In all cases, the procedural mortality was significantly lower than the predicted surgical mortality.

Results of Single-Center Cardiac Database Comparator (Duke University Medical Center):

Nine hundred and fifty three (953) patients in the Duke database with 3+ or 4+ MR were identified as too high risk for surgery using the same high risk criteria as those in the EVEREST II HRR and REALISM studies (i.e. STS mortality risk $\geq 12\%$ or pre-specified surgical risk factors) and managed non-surgically. This made up the cohort of Duke patients, referred to as the Duke Cohort, who were potential candidates for matching to high risk MitraClip patients.

At the time of the Duke analysis, 211 of the 351 patients in the Integrated HSR Cohort had 1-year follow-up. These 211 patients are referred to as the MitraClip Propensity Score Analysis Cohort (MitraClip PSA Cohort). Baseline characteristics of the MitraClip PSA Cohort are compared with that of the 953 patients in the Duke Cohort, as shown in Table 19. Patients in both the MitraClip PSA and the Duke cohorts had a large number of co-morbidities at baseline. As expected, the Integrated HSR Cohort of 351 patients, which included the MitraClip PSA Cohort and 140 additional REALISM HR patients, were similarly high risk in nature. There were some important differences between the Duke and MitraClip patients. MitraClip patients were older on average by 7 years than Duke patients. MitraClip patients were also nearly twice as likely to be classified as NYHA Functional Class III or IV at baseline, than Duke patients, respectively. Mitral regurgitation was primarily of functional etiology in the Duke patients. Likely as a consequence of this, the average LVEF in the Duke patients was lower compared to the MitraClip patients.

These differences in important baseline characteristics and medical history (age, NYHA Functional Class III/IV, LVEF, and MR etiology) necessitated matching in order to make meaningful comparisons of survival between Duke and MitraClip patients.

Table 19: MitraClip PSA Cohort and Duke Cohort – Baseline Demographic Characteristics and Medical History

Characteristic	Integrated HSR Cohort (N = 351) ^a	MitraClip PSA Cohort (N = 211) ^a	Duke Cohort (N = 953)
Age (years), Mean ± SD (N)	75.7±10.5 (351)	76.0 ± 10.3 (211)	68.5 ± 13.2 (953)
Patients over 75 years of age	58.1% (204/351)	57.3% (121/211)	36.1% (344/953)
Female Gender	39.0% (137/351)	39.3% (83/211)	51.1% (487/953)
Prior Myocardial Infarction	50.7% (177/349)	48.8% (102/209)	42.8% (408/953)
Atrial Fibrillation History	68.5% (217/317)	63.6% (124/195)	51.7% (493/953)
Prior Stroke	12.8% (45/351)	14.2% (30/211)	14.7% (140/953)
Diabetes	39.4% (138/350)	40.3% (85/211)	35.5% (338/953)
Moderate to Severe Renal Disease	30.5% (107/351)	30.8% (65/211)	18.5% (176/953)
Chronic Obstructive Pulmonary Disease (w/ Home O2)	11.1% (39/351)	12.3% (26/211)	7.1% (68/953)
Previous Cardiovascular Surgery	59.8% (210/351)	58.3% (123/211)	49.9% (476/953)
NYHA Class III/IV Heart Failure	84.9% (298/351)	85.8% (181/211)	46.6% (440/944)
Functional MR Etiology	70.1% (246/351)	70.6% (149/211)	93.2% (888/953)
LV Ejection Fraction (%), Mean ± SD (N)	47.5 ± 14.2 (318)	49.2 ± 13.7 (201)	36.7 ± 10.9 (953)
LV Internal Diameter systole (cm), Mean ± SD (N)	4.4 ± 1.1 (323)	4.2 ± 1.1 (201)	4.2 ± 1.0 (953)
STS Mortality Risk (%), Mean ± SD (N)	11.3 ± 7.7 (351)	12.2 ± 7.9 (211)	9.7 ± 8.8 (953)

^a MitraClip PSA Cohort was derived by combining 78 EVEREST II HRR patients with 133 REALISM HR patients who were enrolled between January 2009 and February 2010; Integrated HSR Cohort (N = 351) was derived by the addition of 140 REALISM HR patients enrolled between January 2010 and March 2011 to the MitraClip PSA Cohort

Propensity matching was performed based on the nearest available Mahalanobis distance metric within calipers defined by the standard deviation (SD) of the logit of the propensity scores. Matches were obtained for 127 MitraClip patients of the 211 MitraClip PSA Cohort to within a caliper of $0.25 \times$ SDs of the logit of the propensity scores. Matches were obtained for the remaining 84 MitraClip patients by expanding the caliper. These patients were matched to Duke patients with the nearest propensity score.

Baseline characteristics for the matched patients are shown in Table 20. MitraClip and Duke patients are well balanced with respect to most baseline characteristics. However, since matches were obtained outside a narrow caliper of 0.25 SD of the logit of the propensity score for 84 of the 211 patients, some variables (MR etiology, LVEF and LVIDs) were statistically significantly different.

Table 20: Baseline Demographic Characteristics and Medical History – MitraClip and Duke Matched Patients

Characteristic	MitraClip Matched (N = 211)	Duke Matched (N = 211)	p-value
Age (years), Mean \pm SD (N)	76.0 \pm 10.3 (211)	75.1 \pm 7.8 (211)	0.073
Patients over 75 years of age	57.3% (121/211)	52.1% (110/211)	0.282
Female Gender	39.3% (83/211)	46% (97/211)	0.168
Prior Myocardial Infarction	48.8% (102/209)	41.7% (88/211)	0.144
Atrial Fibrillation History	63.6% (124/195)	64.0% (135/211)	0.935
Prior Stroke	14.2% (30/211)	13.7% (29/211)	0.888
Diabetes	40.3% (85/211)	42.2% (89/211)	0.692
Moderate to Severe Renal Disease	30.8% (65/211)	23.2% (49/211)	0.079
Chronic Obstructive Pulmonary Disease (w/ Home O ₂)	12.3% (26/211)	9.5% (20/211)	0.349
Previous Cardiovascular Surgery	58.3% (123/211)	55.9% (118/211)	0.623
NYHA Class III/IV Heart Failure	85.8% (181/211)	79.6% (168/211)	0.094
Functional MR Etiology	70.6% (149/211)	90.0% (190/211)	<0.0001
LV Ejection Fraction (%), Mean \pm SD (N)	49.2 \pm 13.7 (201)	43.6 \pm 9.8 (211)	<0.0001
LV Internal Diameter systole (cm), Mean \pm SD (N)	4.2 \pm 1.1 (201)	3.9 \pm 1.0 (211)	0.0005
STS Mortality Risk (%), Mean \pm SD (N)	12.2 \pm 7.9 (211)	12.9 \pm 9.5(211)	0.801

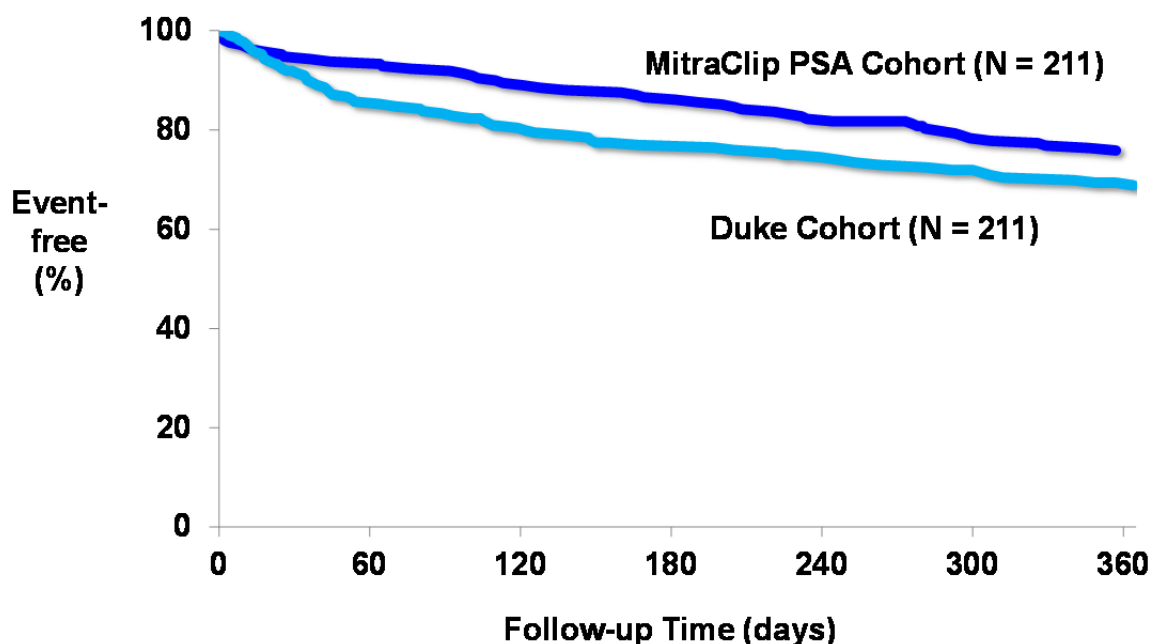
Kaplan-Meier analyses of mortality were performed in the matched cohort. Duration of follow-up for the MitraClip patients was from the date of the procedure to the date of death or 365 days post-procedure, whichever was shorter. Duration of follow-up for the Duke patients was calculated from the date of the echo to the date of death or 365 days post-echo, whichever was shorter.

Figure 11 shows Kaplan-Meier freedom from mortality curves for the MitraClip (N = 211) and the corresponding matches in the Duke cohort. The 30-day and 1-year mortality rates in the MitraClip patients were 5.3% and 24.1%, respectively. The corresponding rates in the Duke patients were 8.1% and 31.2%, respectively. The unadjusted log-rank p-value comparing survival in the two groups was 0.08 (Table 21). Since differences in MR etiology, LVEF and LVIDs between the two groups were statistically significant, an adjusted analysis was performed using Cox proportional hazards regression. The model included MR etiology, LVEF and LVIDs in addition to treatment received. The hazard ratio for MitraClip to Duke for all-cause mortality at 1 year in this adjusted analysis was 0.69 (95% CI: [0.46, 1.04], p = 0.08).

Table 21: Estimates from the Cox Model Adjusted for baseline LVIDs, LVEF and MR Etiology - Cohort 3

Effect	HR (95% CI)	p-value
Degenerative MR	1.45 (0.84, 2.49)	0.183
LVIDs (cm)	1.07 (0.83, 1.38)	0.607
LVEF (%)	0.99 (0.97, 1.01)	0.389
MitraClip	0.69 (0.46, 1.04)	0.080

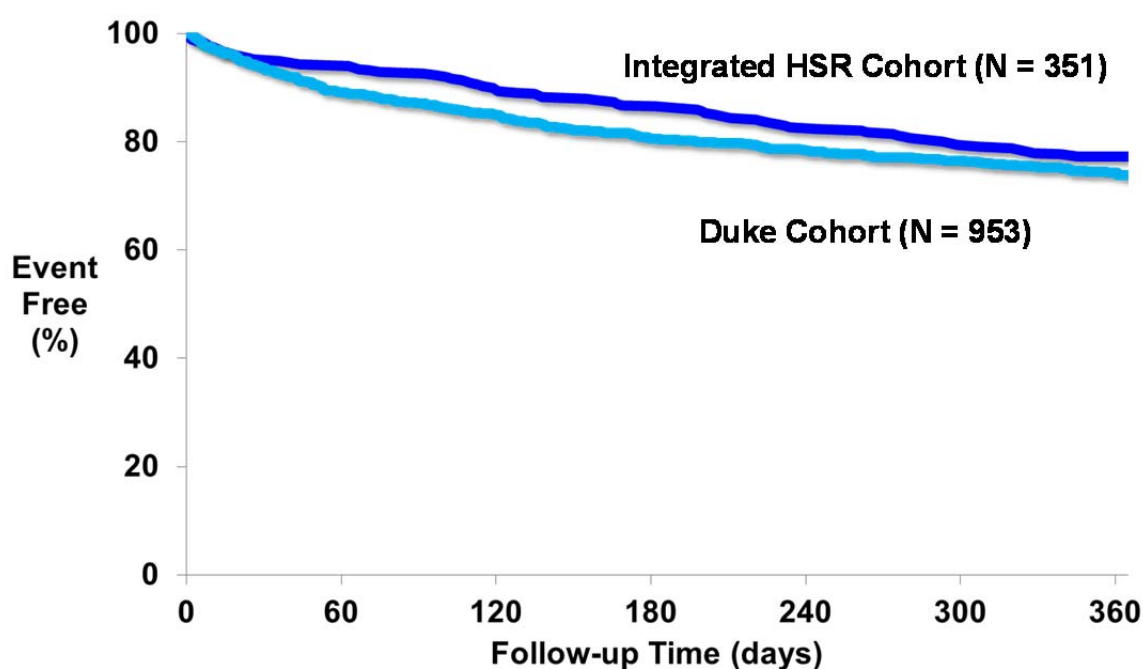
Figure 11: Kaplan-Meier Survival - MitraClip PSA Cohort (N = 211) and Duke Cohort (N = 211)



Duke Cohort				
Time Post Echo	Baseline	30-Day	1-Year	
# At Risk	211	192	133	
# Events	0	17	64	
% Event Free	100%	91.9%	68.8%	
95% Confidence Interval	-	(87.3%, 94.9%)	(62.0%, 74.7%)	
MitraClip PSA Cohort				
Time Post Index Procedure	Baseline	30-Day	1-Year	
# At Risk	211	198	154	
# Events	0	11	50	
% Event Free	100%	94.7%	75.9%	
95% Confidence Interval	-	(90.7%, 97.1%)	(69.4%, 81.2%)	

In addition to survival comparison in the matched cohort, a descriptive comparison of the full Integrated HSR Cohort (N = 351) to the full Duke Cohort (N = 953) is provided below (Figure 12). The hazard ratio from the unadjusted analysis was 0.72 (95% CI:[0.65, 1.08]). The results from the unadjusted analysis in the full cohorts remain consistent with the results from the more closely matched cohort, despite differences in several baseline co-morbidities being biased against the MitraClip.

Figure 12: Kaplan-Meier Survival - Integrated HSR Cohort (N = 351) and Duke Cohort (N = 953)



Duke Cohort				
Time Post Echo	Baseline	30-Day	1-Year	
# At Risk	953	875	642	
# Events	0	61	241	
% Event Free	100%	93.5%	73.8%	
95% Confidence Interval	-	(91.8%, 94.9%)	(70.9%, 76.6%)	
Integrated HSR Cohort				
Time Post Index Procedure	Baseline	30-Day	1-Year	
# At Risk	351	329	257	
# Events	0	17	78	
% Event Free	100%	95.1%	77.2%	
95% Confidence Interval	-	(92.2%, 96.9%)	(72.3%, 81.3%)	

The point estimates for the hazard ratio in the matched analysis as well as in the full cohorts were in favor of the MitraClip. In addition, the upper confidence bounds for the hazard ratios were 1.04 and 1.08 in the matched cohort and in the full cohorts, respectively. In the worst case, these upper confidence bounds represent a tolerable mortality risk compared to the natural history of the disease for a high surgical risk population with limited treatment options for MR reduction.

A full report on the Duke analysis, including details on the matching methodology and results is provided in Appendix H.

8.3.5.4 Integrated High Surgical Risk Cohort Secondary Safety Results

Components of the major adverse event (MAE) endpoint, and the overall rate at 30 days and 1 year are summarized in Table 22. Strokes occurred in 2.6% of patients at 30 days and 3.4% at 1 year. Five of the 17 deaths that occurred within 30 days occurred in patients who experienced stroke post-MitraClip procedure. Two additional 30 day stroke patients died through one year. Despite approximately 30% of patients having renal dysfunction at baseline, renal failure occurred in only 1.7% of patients at 30 days. Myocardial infarction occurred in 1.1% of patients at 30 days. There was only 1 occurrence (0.6%) of non-elective cardiovascular surgery for adverse events. This patient underwent an attempted MitraClip procedure, however, no device was implanted due to an inability to grasp the leaflets which resulted in leaflet damage. The patient underwent urgent mitral valve replacement surgery one day following the MitraClip procedure, and was discharged home after surgery. The patient expired one month after completing 2-year follow-up. As transfusions occur at a high rate in both groups, the overall MAE rate is also presented with transfusion events excluded. The MAE rate excluding transfusion events at 30 days was 9.1%.

At 1 year, MAEs occurred at a rate of 37.6% in the Integrated HSR Cohort with deaths composing the majority of events. However, comparisons to the Duke cohort demonstrated that there was no elevated risk of mortality from the MitraClip procedure in patients who are too high risk for surgery at 1 year.

Table 22: Integrated HSR Cohort (N = 351) - CEC Adjudicated Major Adverse Events

Description of Event	% Patients (n/N)	
	30-Day	1-Year
Death	4.8% (17/351)	22.8% (80/351)
Myocardial infarction	1.1% (4/351)	2.3% (8/351)
Re-operation for failed surgical repair or replacement	0.0% (0/351)	0.0% (0/351)
Non-elective cardiovascular surgery for adverse events	0.3% (1/351)	0.3% (1/351)
Stroke	2.6% (9/351)	3.4% (12/351)
Renal Failure	1.7% (6/351)	5.4% (19/351)
Deep wound infection	0.0% (0/351)	0.0% (0/351)
Ventilation > 48 hours	2.8% (10/351)	5.4% (19/351)
GI complication requiring surgery	0.3% (1/351)	1.4% (5/351)
New onset of permanent AF	0.3% (1/351)	0.3% (1/351)
Septicemia	0.9% (3/351)	4.3% (15/351)
Transfusion ≥ 2 units	13.4% (47/351)	22.5% (79/351)
Total^a	18.8% (66/351)	37.6% (132/351)
Total^a (Excluding Transfusions ≥ 2 units)	9.1% (32/351)	27.9% (98/351)

^a Total number of patients may not equal the sum of patients in each row since one patient may experience multiple events.

Other secondary safety endpoints are summarized in Table 23. Major bleeding was defined as bleeding requiring transfusion of 2 or more units of blood or requiring surgical intervention. Major bleeding complications occurred at 9.7% at 30 days with few events occurring beyond 30 days in the Integrated HSR Cohort. The large majority (21) of 30-day bleeding events were related to access site bleeding. Five patients experienced GI bleed, 2 of which were due to endotracheal tube trauma from the transesophageal echocardiogram, 1 patient experienced tamponade during the transseptal procedure due to which the MitraClip procedure was aborted, 1 patient experienced intracerebral hemorrhage (also reported as a stroke in the MAE table), 4 patients had chest wall/thorax bleeds associated with cardiac surgery, and 2 patients experienced bleeding from an unknown location.

Major vascular complications occurred at a relatively low rate (3.4%) at 30 days likely due to access to the mitral valve via the femoral vein and inferior vena cava. Vascular complications related to the procedure included 4 hematomas, 5 access site repairs, and 3 AV fistula.

There was one non-cerebral thromboembolism at 30 days, and one additional event occurred through 1 year. There was no endocarditis, thrombosis, or hemolysis at 30 days and only 1 case of endocarditis reported at 1 year. Residual ASD requiring mechanical closure occurred in a total of 11 patients, 6 within 30 days and an additional 5 by 1 year. New onset of persistent atrial fibrillation occurred in 2.6% at 30 days and 6.8% by 1 year. Heart block or other arrhythmia requiring a permanent pacemaker implant occurred in 1.1% of patients at 30 days and 2.6% at 1 year.

In a patient population with a complex, comorbid profile, such as the Integrated HRS Cohort, these event rates are not unexpected.

Table 23: Integrated HSR Cohort (N = 351) – Other Secondary Safety Events

Description of Event	% Patients (n/N)	
	30-Day	1-Year
Major Bleeding Complication	9.7% (34/351)	11.7% (41/351)
Major Vascular Complication	3.4% (12/351)	4.0% (14/351)
Non-Cerebral Thromboembolism	0.3% (1/351)	0.6% (2/351)
Endocarditis	0.0% (0/351)	0.3% (1/351)
Thrombosis	0.0% (0/351)	0.0% (0/351)
Hemolysis	0.0% (0/351)	0.0% (0/351)
Atrial Septal Defect requiring intervention	1.7% (6/351)	3.1% (11/351)
Persistent Atrial Fibrillation, New Onset	2.6% (9/351)	6.8% (24/351)
Heart Block/Other arrhythmia requiring permanent pacemaker	1.1% (4/351)	2.6% (9/351)

^a CEC adjudicated for the 78 EVEREST II HRR patients; events for the 273 REALISM cohort are site reported

8.3.5.5 Integrated High Surgical Risk Cohort Post-Procedure Device Complications

Post-procedure complications specifically related to the MitraClip Device occurred at a low rate. Single leaflet device attachments (SLDA) occur when the MitraClip remains attached to one valve leaflet and loses attachment to the other leaflet. Most cases of SLDA take place early and occurred in 6 patients within 30 days. Only two additional patients experienced SLDA after 30 days. Three of the 8 patients who experienced SLDA underwent successful mitral valve surgery and 4 underwent a successful second MitraClip procedure. Six of the 7 secondary interventions had successful MR reduction to 2+ or less. There was no further intervention in 1 patient. The patient subsequently died due to cardiopulmonary arrest, myocardial infarction and coronary artery disease.

There were no device embolizations at any follow-up time for the Integrated HSR Cohort.

Mitral valve stenosis, defined as Echocardiography Core Lab (ECL) measured mitral valve orifice area $< 1.5 \text{ cm}^2$, is a rare complication following treatment with the MitraClip. No mitral valve stenosis occurred through 30 days. Mitral valve stenosis was reported in 3 patients after 30 days:

- Stenosis was reported at 3 years in 1 patient with a history of rheumatic disease. The patient successfully underwent mitral valve replacement surgery.
- Two patients had ECL measured mitral valve orifice area $< 1.5 \text{ cm}^2$ at 6 months and 18 months respectively. Both patients remain in the study and have not undergone mitral valve surgery.

Table 24: Integrated HSR Cohort – Post-Procedural Device Complications

Complication	% Patients (n/N)	
	Early (through 30 days)	Late (> 30 days)
Single Leaflet Device Attachment	1.7% (6/351)	0.6% (2/351)
Mitral Valve Surgery (N = 3)	0.3% (1/351)	0.6% (2/351)
2 nd MitraClip procedure (N = 4)	1.1% (4/351)	0.0% (0/351)
MitraClip Embolizations	0.0% (0/351)	0.0% (0/351)
Mitral Valve Stenosis	0.0% (0/351)	0.9% (3/351)

8.3.5.6 Integrated High Surgical Risk Cohort Safety Outcomes by Patient Subgroups

The EVEREST II HRR and REALISM studies enrolled both male and female patients, patients with either degenerative (DMR) or functional (FMR) MR etiologies and patients with STS mortality risk $\geq 12\%$ or $< 12\%$. In order to assess the impact of heterogeneity on safety, subgroup analyses were performed.

8.3.5.6.1 Integrated High Surgical Risk Cohort Safety Outcomes by MR Etiology

Patients with degenerative MR (DMR) were older than patients with functional MR (FMR) and the majority of DMR patients (81%) were over 75 years of age (Table 26). Large proportions of both DMR and FMR patients had coronary artery disease. Similar proportions of DMR and FMR patients had moderate to severe renal disease and atrial fibrillation history. Half of DMR patients and greater than 60% of FMR patients had undergone a previous cardiovascular surgery. As expected, a larger proportion of FMR patients than DMR patients had a history of myocardial infarction at baseline. The mean LVEF in DMR patients was higher and the mean LVIDs was lower than in FMR patients. Due to protocol exclusion criteria, neither group had severe left ventricular dysfunction at baseline.

Procedural mortality was significantly lower than both predicted surgical mortality as defined in the protocol and the STS mortality risk in DMR or FMR patients (Table 25). The MAE rates at 30 days observed in the DMR and FMR subgroups were comparable (18.1% in DMR vs. 19.1% in FMR). Mortality at 30 days was slightly higher in DMR patients (6.7%) compared to FMR patients (4.1%). This is not unexpected since DMR patients were older on average by 9 years than FMR patients, with many of the same baseline co-morbidities. At 1 year, MAE rates remained comparable (36.2% in DMR vs. 38.2% in FMR), with mortality being the primary driver.

Table 25: Integrated HSR Cohort – Primary Safety Endpoint by MR Etiology

	Degenerative MR (N = 105)	Functional MR (N = 246)
Observed Procedural Mortality	6.7% (7/105)	4.1% (10/246)
97.5% Upper Confidence Bound (UCB) ^a	13.3%	7.3%
Average Predicted Surgical Mortality (STS or Surgeon Assessed)	17.7% (p = 0.0007)	18.4% (p < 0.0001)
Average Predicted Surgical Mortality (STS Mortality Risk)	13.1% (p = 0.0239)	10.6% (p = 0.0001)

^a UCB is based on the Clopper-Pearson method
p-values obtained by Monte-Carlo simulations

Table 26: Integrated HSR Cohort – Baseline Characteristics and Safety Outcomes by MR Etiology

Characteristic	Degenerative MR (N = 105)	Functional MR (N = 246)
Mean Age	81.8 yrs	73.2 yrs
Patients over 75 years of age	81.0%	48.4%
Female Gender	40.0%	38.6%
Coronary Artery Disease	74.8%	85.4%
Prior Myocardial Infarction	29.5%	59.8%
Atrial Fibrillation History	71.6%	67.0%
Prior Stroke	9.5%	14.2%
Diabetes	29.5%	43.7%
Moderate to Severe Renal Disease	26.7%	32.1%
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	28.5%	29.0%
Hypertension	89.5%	89.4%
Previous Cardiovascular Surgery	50.4%	63.8%
Previous Percutaneous Coronary Intervention	35.2%	56.1%
NYHA Class III/IV Heart Failure	81.9%	86.2%
Mean LV Ejection Fraction	61.0%	41.7%
Mean LV Internal Diameter systole	3.4 cm	4.7 cm
Safety Outcome	Degenerative MR (N = 105)	Functional MR (N = 246)
30-Day Mortality, %	6.7%	4.1%
30-Day MAE, %	18.1%	19.1%
30-Day MAE (excluding transfusions) , %	8.6%	9.3%
30-Day Major Bleeding Complication, %	11.4%	8.9%
30-Day Major Vascular Complication, %	2.9%	3.7%
1-Year Mortality, %	23.8%	22.4%
1-Year MAE, %	36.2%	38.2%
1-Year MAE (excluding transfusions) , %	26.7%	28.5%

8.3.5.6.2 Integrated High Surgical Risk Cohort Safety Outcomes by Sex

Both male and female patients were elderly. Large proportions of both male and female patients had coronary artery disease and atrial fibrillation history. Similar proportions of male and female patients had moderate to severe renal disease and prior stroke. A previous myocardial infarction was reported more often in males than females. Nearly 70% of male patients and 45% of female patients had undergone a previous cardiovascular surgery. The higher rate of surgery for males is consistent with national trends for cardiac surgery.

Procedural mortality was significantly lower than both predicted surgical mortality as defined in the protocol and the STS mortality risk in male or female patients (Table 25).

Table 27: Integrated HSR Cohort – Primary Safety Endpoint by Sex

	Males (N = 214)	Females (N = 137)
Observed Procedural Mortality	4.7% (10/214)	5.1% (7/137)
97.5% Upper Confidence Bound ^a	8.4%	10.2%
Average Predicted Surgical Mortality (STS or Surgeon Assessed)	18.1% (p < 0.0001)	18.4% (p < 0.0001)
Average Predicted Surgical Mortality (STS Mortality Risk)	10.9% (p = 0.0008)	12.1% (p = 0.0038)

^a Upper Confidence Bound is based on the Clopper-Pearson method
p-values obtained by Monte-Carlo simulations

The MAE rates at 30 days observed in female patients were higher (25.5%) than in male patients (14.5%). This difference was driven primarily by the rate at which transfusions of ≥ 2 units of blood occurred in females and males (20.4% vs. 8.9%, respectively). More transfusions in females than in males were for reasons unrelated to bleeding, such as anemia, hemolysis and prophylaxis (10 of 28 transfusions in females versus 5 of 19 transfusions in males were unrelated to bleeding). MAE rates excluding transfusions were comparable at 1 year (29.9% vs. 24.8%, respectively) between males and females. Mortality at 1 year in males was higher than in females. At 1 year, survival in males (75.2%) was lower than in females (80.4%). The higher mortality rate in males is not surprising since males were slightly older than females and had undergone prior cardiovascular surgery more often than females.

Table 28: Integrated HSR Cohort – Baseline Characteristics and Safety Outcomes by Sex

Characteristic	Males (N = 214)	Females (N = 137)
Mean Age	76.5 yrs	74.6 yrs
Patients over 75 years of age	60.7%	54.0%
Coronary Artery Disease	89.3%	71.1%
Prior Myocardial Infarction	56.6%	41.6%
Atrial Fibrillation History	72.0%	62.9%
Prior Stroke	12.6%	13.1%
Diabetes	36.9%	43.4%
Moderate to Severe Renal Disease	33.2%	26.3%
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	29.0%	28.7%
Hypertension	88.3%	91.2%
Previous Cardiovascular Surgery	69.6%	44.5%
Previous Percutaneous Coronary Intervention	51.9%	46.7%
NYHA Class III/IV Heart Failure	81.8%	89.8%
Mean LV Ejection Fraction	46.4%	49.1%
Mean LV Internal Diameter systole	4.6 cm	4.0 cm
Safety Outcome	Males (N = 214)	Females (N = 137)
30-Day Mortality, %	4.7%	5.1%
30-Day MAE, %	14.5%	25.5%
30-Day MAE (excluding transfusions) , %	7.9%	10.9%
30-Day Major Bleeding Complication, %	7.5%	13.1%
30-Day Major Vascular Complication, %	3.3%	3.6%
1-Year Mortality, %	25.7%	18.2%
1-Year MAE, %	39.3%	35.0%
1-Year MAE (excluding transfusions) , %	29.9%	24.8%

8.3.5.6.3 Integrated HSR Cohort Safety Outcomes by STS Risk $\geq 12\%$ and $< 12\%$

Patients in STS $\geq 12\%$ were older than those with STS $< 12\%$ by approximately 10 years. Large proportions of both groups had coronary artery disease and atrial fibrillation history. Moderate to severe renal disease occurred at a higher rate in patients with STS $\geq 12\%$. Prior stroke and previous myocardial infarction occurred at the same rate in the two groups. The majority of patients in both groups had undergone a prior cardiovascular surgery.

Procedural mortality was significantly lower than predicted surgical mortality as defined in the protocol and the STS mortality risk in patients with STS mortality risk $\geq 12\%$ or $< 12\%$ (Table 25).

Table 29: Integrated HSR Cohort – Primary Safety Endpoint By STS Risk

	STS $\geq 12\%$ (N = 151)	STS $< 12\%$ (N = 200)
Observed Procedural Mortality	7.3% (11/15)	3.0% (6/200)
97.5% Upper Confidence Bound (UCB) ^a	12.7%	6.4%
Average Predicted Surgical Mortality (STS or Surgeon Assessed)	18.1% (p < 0.0001)	18.3% (p < 0.0001)
Average Predicted Surgical Mortality (STS Mortality Risk)	18.1% (p < 0.0001)	6.2% (p < 0.0307)

^a UCB is based on the Clopper-Pearson method
p-values obtained by Monte-Carlo simulations

MAE rates at 30 days observed in the STS $\geq 12\%$ group were higher (25.8%) than in the STS $< 12\%$ group (13.0%). MAE rates excluding transfusions remained higher in the STS $\geq 12\%$ group than the STS $< 12\%$ group. MAE rates excluding transfusions remained higher at 1 year in the STS $\geq 12\%$ than the STS $< 12\%$ group (32.5% vs. 24.5%). Mortality in the STS $\geq 12\%$ group was higher (27.0%) than in the STS $< 12\%$ group (19.5%). These results are not unexpected since the STS $\geq 12\%$ were older on average by 10 years and had a higher incidence of a subset of the co-morbidities than the STS $< 12\%$ group.

Table 30: Integrated HSR Cohort – Baseline Characteristics and Safety Outcomes by STS Risk $\geq 12\%$ and $< 12\%$

Characteristic	STS $\geq 12\%$ (N = 151)	STS $< 12\%$ (N = 200)
Mean Age	81.1 yrs	71.7 yrs
Patients over 75 years of age	76.8%	44.0%
Female Gender	46.4%	33.5%
Coronary Artery Disease	81.2%	83.0%
Prior Myocardial Infarction	50.0%	51.3%
Atrial Fibrillation History	75.9%	62.8%
Prior Stroke	13.9%	12.0%
Diabetes	45.3%	35.0%
Moderate to Severe Renal Disease	47.7%	17.5%
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	31.7%	26.6%
Hypertension	95.4%	85.0%
Previous Cardiovascular Surgery	51.7%	66.0%
Previous Percutaneous Coronary Intervention	49.7%	50.0%
NYHA Class III/IV Heart Failure	92.7%	79.0%
Mean LV Ejection Fraction	50.1%	45.3%
Mean LV Internal Diameter systole	4.0 cm	4.6 cm
Safety Outcome	STS $\geq 12\%$ (N = 151)	STS $< 12\%$ (N = 200)
30-Day Mortality, %	7.3%	3.0%
30-Day MAE, %	25.8%	13.5%
30-Day MAE (excluding transfusions) , %	12.6%	6.5%
30-Day Major Bleeding Complication, %	15.2%	5.5%
30-Day Major Vascular Complication, %	4.6%	2.5%
1-Year Mortality, %	26.5%	20.0%
1-Year MAE, %	45.0%	32.0%
1-Year MAE (excluding transfusions) , %	32.5%	24.5%

8.3.6 Integrated High Surgical Risk Cohort Effectiveness Results

8.3.6.1 Integrated High Surgical Risk Cohort Implant Success

Implant success rate was high (336/351 or 95.7%) in the Integrated HSR Cohort. Physicians had the option of deploying 2 MitraClip devices if a single Device did not provide satisfactory MR reduction and the mitral valve area was large enough to allow a second MitraClip device to be placed without resulting in mitral stenosis. One MitraClip Device was implanted in 57.3% (201/351) and 2 devices were implanted in 38.5% (135/351) of

patients. Reasons for unsuccessful implants in the 15 patients were mostly due to technical reasons including the inability to grasp the leaflets (5), inability to adequately reduce MR (3), or a mitral valve area that was not adequate to accommodate the device without creating mitral stenosis (3) or the septum could not be crossed (1). There were rare cases where an unsuccessful implant was due to safety related reasons, including one case each of vascular complications, tamponade or the presence of thrombus (noted on the procedural transesophageal echocardiogram resulting in discontinuation of the procedure).

Table 31: Integrated HSR Cohort – Reason for Unsuccessful Implant

Reason	Reason for Unsuccessful Implant
Inability to grasp leaflets	1.4% (5/351)
Inability to adequately reduce MR	0.9% (3/351)
Mitral valve area not adequate	0.9% (3/351)
Unable to cross septum	0.3% (1/351)
Vascular complication	0.3% (1/351)
Cardiac tamponade	0.3% (1/351)
Right atrial thrombus	0.3% (1/351)

8.3.6.2 Integrated High Surgical Risk Cohort MR Severity by Echocardiography

Determination of MR severity was performed by an independent echocardiography core laboratory following the American Society of Echocardiography guidelines (Appendix A).

Table 32 shows accountability for MR severity at baseline and discharge. It is noted that 327 patients are evaluable at baseline and discharge.

Table 32: Integrated HSR Cohort – Accountability for MR Severity at Baseline and Discharge

Baseline MR	Discharge MR				Total
	Evaluable	Missing	Death	Withdrawn	
Evaluable	327	7	0	3	337
Missing	13	1	0	0	14
Total	340	8	0	3	351

Table 33 shows MR severity at baseline and discharge. Patients who died were assumed to have not experienced reduction to $MR \leq 2+$ and were included only in the denominator for assessment of MR reduction. This analysis did not account for 24 patients with missing MR reads either at baseline or discharge. Improvements to $MR \leq 1+$ were observed in 47.3% patients with baseline MR of 3+ and in 38.3% patients with baseline MR of 4+. Improvements to $MR \leq 2+$ were observed in a larger proportion of patients with MR of either 3+ (86.6%) or 4+ (76.6%).

Table 33: Integrated HSR Cohort - MR Severity at Baseline and Discharge

Baseline MR	Discharge MR					Evaluable
	≤1+	2+	3+	4+	Missing due to Death	
1+	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	2
2+	23 (53.5%)	18 (41.9%)	2 (4.7%)	0 (0%)	0 (0%)	43
3+	95 (47.3%)	79 (39.3%)	17 (8.5%)	8 (4%)	2 (1%)	201
4+	31 (38.3%)	31 (38.3%)	16 (19.8%)	3 (3.7%)	0 (0%)	81
Evaluable	150 (45.9%)	129 (39.4%)	35 (10.7%)	11 (3.4%)	2 (0.6%)	327

Table 34 shows accountability for MR severity at discharge and 1 year. It is noted that 309 patients are evaluable at discharge and 1 year.

Table 34: Integrated HSR Cohort – Accountability for MR Severity at Discharge and 1 Year

Discharge MR	1-Year MR				
	Evaluable	Missing	Death	Withdrawn	Total
Evaluable	309	19	0	10	338
Missing	3	0	3	5	11
Death	0	0	2	0	2
Total	312	19	5	15	351

^a Of these 5 patients, 2 who died without a discharge MR read are not accounted for at 1 year

Table 35 shows MR severity at discharge and 1 year. Patients who died were assumed to have not experienced reduction to MR ≤ 2+ and were included only in the denominator for assessment of durability of MR reduction. This analysis did not account for patients with missing MR reads either at discharge or 1 year. MR ≤ 1+ was sustained at 1 year in 36.7% of patients with discharge MR ≤ 1+. MR ≤ 2+ was sustained in a larger proportion of patients (68.3%). Of patients who achieved MR ≤ 1+ at discharge, 69.4% had MR ≤ 2+ at 1 year.

Table 35: Integrated HSR Cohort - MR Grade at Discharge and 1 Year

Discharge MR	1-Year MR					Evaluable
	≤1+	2+	3+	4+	Missing due to Death	
1+	54 (36.7%)	48 (32.7%)	13 (8.8%)	0 (0%)	32 (21.8%)	147
2+	26 (22.0%)	53 (44.9%)	10 (8.5%)	3 (2.5%)	26 (22.0%)	118
3+	6 (17.6%)	7 (20.6%)	5 (14.7%)	5 (14.7%)	11 (32.4%)	34
4+	0 (0%)	1 (10%)	0 (0%)	1 (10%)	8 (80%)	10
Evaluable	86 (27.8%)	109 (34.7%)	28 (8.8%)	9 (2.8%)	77 (25.9%)	309

These analyses were repeated using a parametric failure model for the composite of (1) death and MR > 2+, and (2) death and MR > 1+ at 1 year. See Appendix G for event-free survival curves.

MR severity at baseline and discharge from 325 patients with interpretable echoes at both timepoints in the Integrated HSR Cohort is summarized in Table 36. This analysis did not account for 26 patients who died or had missing MR reads either at baseline or discharge. Improvements to MR ≤ 1+ were observed in 47.7% surviving patients with baseline MR of 3+ and in 38.2% surviving patients with baseline MR of 4+. Improvements to MR ≤ 2+ were observed in a larger proportion of surviving patients with MR of either 3+ (87.3%) or 4+ (76.4%).

**Table 36: Integrated HSR Cohort – ECL Assessed MR Severity at Baseline and Discharge
Surviving Patients with Paired Data at Baseline and Discharge**

Baseline MR	Discharge MR				Total
	≤1+	2+	3+	4+	
1+	1 (50.0%)	1 (50.0%)	-	-	2
2+	23 (53.4%)	18 (41.8%)	2 (4.6%)	-	43
3+	95 (47.7%)	79 (39.7%)	17 (8.5%)	8 (4.0%)	199
4+	31 (38.2%)	31 (38.2%)	16 (19.7%)	3 (3.7%)	81
Total	150 (46.2%)	129 (39.7%)	35 (10.8%)	11 (3.4%)	325

Table 37 shows MR severity at discharge and 1 year in patients surviving to 1 year with complete data at discharge and 1 year. This analysis did not account for 119 patients who died or had missing MR reads either at discharge or 1 year. MR \leq 1+ was sustained at 1 year in 54% of patients with discharge MR \leq 1+. MR \leq 2+ was sustained in a larger proportion of patients (87.4%). Of surviving patients who achieved MR \leq 1+ at discharge, 95.7% had MR \leq 2+ at 1 year.

**Table 37: Integrated HSR Cohort - MR Grade at Discharge and 1 Year
Surviving Patients with Patients with Paired Data at Discharge and 1 Year**

Discharge MR	1-Year MR				Total
	\leq 1+	2+	3+	4+	
1+	54 (47.0%)	48 (41.7%)	13 (11.3%)	0	115
2+	26 (28.3%)	53 (57.6%)	10 (10.9%)	3 (3.3%)	92
3+	6 (26.0%)	7 (30.4%)	5 (21.7%)	5 (21.7%)	23
4+	0 (0%)	1 (50.0%)	0 (0%)	1 (50.0%)	2
Total	86 (37.1%)	109 (47.0%)	28 (12.1%)	9 (3.9%)	232

These data show that the MitraClip Device successfully reduces MR severity, which remains durable through 1 year in a large proportion of patients. In the analysis that accounted for patients who died by 1 year, there remained a significant proportion of patients in whom MitraClip was beneficial.

8.3.6.3 Integrated High Surgical Risk Cohort Major Effectiveness Endpoint Results

Left Ventricular Measurements

Table 38 is an example of accountability for left ventricular measurements at baseline and 1 year. When an echocardiogram is available, all left ventricular measurements may not be evaluable by the ECL. It is noted that 203 patients are evaluable at baseline and 1 year for left ventricular end diastolic volume (LVEDV).

Table 38: Integrated HSR Cohort – Accountability for LVEDV at Baseline and 1 Year

Baseline LVEDV	1-Year LVEDV				Total
	Evaluable	Missing due to Death	Missing due to other reasons	Withdrawn	
Evaluable	203	74	28	14	319
Missing	14	8	9	1	32
Total	217	82	37	15	351

Left ventricular measurements at baseline and 1 year in 203 surviving patients with ECL assessed measurements at both timepoints are summarized in Table 39. The table demonstrates statistically significant reduction in all four left ventricular measurements. On average, patients experienced a reduction of 18 ml in left ventricular end diastolic volume at 1 year. Left ventricular end systolic volume decreased by 8 ml at 1 year.

Table 39: Integrated HSR Cohort – Left Ventricular Size at Baseline and 1 Year Surviving Patients with Paired Data at Baseline and 1 Year

LV Measurement	N	Baseline	1 Year	Difference (1 Year - Baseline)	p-value
LVEDV, ml					
Mean ± SD	203	160.5 ± 55.9	142.6 ± 53.1	-17.9 ± 31.8	<0.001
LVIDd, cm					
Mean ± SD	221	5.6 ± 0.8	5.4 ± 0.8	-0.2 ± 0.4	<0.001
LVESV, ml					
Mean ± SD	202	87.0 ± 46.8	78.9 ± 43.9	-8.1 ± 23.2	<0.001
LVIDs cm					
Mean ± SD	210	4.3 ± 1.1	4.1 ± 1.1	-0.1 ± 0.6	0.002

The reductions in the left ventricular end diastolic and systolic volumes were greater in patients with greater reductions in MR at 1 year (Table 40). In patients with the largest reductions in MR (from 3+/4+ to ≤ 1+), there were larger reductions in left ventricular end diastolic and systolic volumes, findings that strongly support the conclusion that the improvements in MR resulted in significant improvement in cardiac function.

Table 40: Integrated HSR Cohort - Change in Left Ventricular at 1 Year by MR Patients Surviving at 1 Year with Baseline 3+/4+ MR

Change in Left Ventricular Measurement	1-Year MR		
	≤ 1+	2+	3+/4+
LVEDV, ml			
N	63	77	32
Mean	-26.5	-18.7	-10.5
(95% Conf Int)	(-34.9, -18.2)	(-25.5, -11.9)	(-23.1, 2.2)
LVIDd, ml			
N	68	88	33
Mean	-0.3	-0.2	-0.1
(95% Conf Int)	(-0.4, -0.1)	(-0.3, -0.1)	(-0.2, 0.0)
LVESV, ml			
N	63	77	32
Mean	-13.9	-5.6	-5.4
(95% Conf Int)	(-20.4, -7.4)	(-10.3, -0.9)	(-13.6, 2.8)
LVIDs, ml			
N	66	82	31
Mean	-0.2	-0.0	-0.0
(95% Conf Int)	(-0.4, -0.1)	(-0.1, 0.1)	(-0.2, 0.2)

Patients who expired before reaching 1-year follow-up or patients with missing data at 1 year (due to unevaluable echo, missed visit or early withdrawal) were excluded from the analysis of left ventricular measurements. It was important to evaluate the bias from excluding these patients. The following sensitivity analyses were therefore performed:

- Last Observation Carried Forward (LOCF) for all patients with missing data. Patients with missing data at baseline were excluded
- Since patients who died at 1 year may have worsened after the last measurement was obtained, the following imputation was performed. Patients with missing data at baseline were excluded:
 - For patients who died: The mean and standard deviation for patients whose volumes and dimensions increased over baseline across any time were used to randomly generate changes at 1 year. For patients with more than one worsened measurement, the maximum was used in the calculation of the mean and standard deviation.
 - For patients with missing data for other reasons, the last observation was carried forward.

Both sensitivity analyses (Table 41 and Table 42) show that left ventricular measurements (LVEDV, LVIDd and LVESV) demonstrate reductions from baseline.

**Table 41: Integrated HSR Cohort – Sensitivity Analyses for LV Measurements
LOCF for all Patients with Baseline Data Available**

LV Measurement	N	Difference (1-Year - Baseline)	p-value
LVEDV, ml			
Mean ± SD	319	-15.3 ± 29.3	< 0.0001
LVIDd, cm			
Mean ± SD	331	-0.2 ± 0.4	< 0.0001
LVESV, ml			
Mean ± SD	318	-6.3 ± 22.0	< 0.0001
LVIDs, cm			
Mean ± SD	323	-0.1 ± 0.5	0.0001

**Table 42: Integrated HSR Cohort – Sensitivity Analyses for LV Measurements
Deaths Assumed to have Worsened LV Measurement; LOCF for Other Missing**

LV Measurement	N	Difference (1-Year - Baseline)	p-value
LVEDV, ml			
Mean ± SD	319	-9.4 ± 30.3	< 0.0001
LVIDd, cm			
Mean ± SD	331	-0.1 ± 0.4	< 0.0001
LVESV, ml			
Mean ± SD	318	-2.3 ± 22.6	0.036
LVIDs, cm			
Mean ± SD	323	0.0 ± 0.5	0.541

NYHA Class

Table 32 shows accountability for NYHA Class at baseline and 1 year, noting that 234 patients are evaluable at baseline and 1 year.

Table 43: Integrated HSR Cohort – Accountability for NYHA Class at Baseline and 1 Year

	1-Year NYHA				Total
	Evaluable	Missing due to death	Missing due to other reasons	Withdrawn	
Evaluable	234	83	19	15	351

Table 44 shows NYHA Class at baseline and 1 year, accounting for deaths that occurred through 1 year. Of the 351 patients in the Integrated HSR Cohort, paired data were available on 234 patients. The table shows that accounting for deaths, 26.5% of patients experienced

an improvement by at least 2 classes at 1 year, and 59.6% were in NYHA Class I or II and experienced an improvement of at least 1 class at 1 year.

Table 44: Integrated HSR Cohort – NYHA Class at Baseline and 1 Year

Baseline NYHA	1-Year NYHA					Evaluable
	I	II	III	IV	Missing due to death	
I	4 (50.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)	8
II	18 (41.9%)	17 (39.5%)	1 (2.3%)	0 (0.0%)	7 (16.3%)	43
III	54 (27.6%)	69 (35.2%)	24 (12.2%)	2 (1.0%)	47 (24.0%)	196
IV	12 (17.1%)	18 (25.7%)	11 (15.7%)	2 (2.9%)	27 (38.6%)	70
Evaluable	88 (27.8%)	106 (33.4%)	36 (11.4%)	4 (1.3%)	83 (26.2%)	317

Table 45 shows NYHA Class at baseline and 1 year in patients surviving to 1 year with complete data at baseline and 1 year. This analysis did not account for 117 patients who died or had missing NYHA Class at 1 year. At 1 year, there was a large improvement in NYHA Class, with only 17.1% of patients being in NYHA Class III or IV. More than a third (35.9%) of patients experienced an improvement of at least 2 classes at 1 year, and 73.1% were in NYHA Class I or II and experienced an improvement of at least 1 class at 1 year.

**Table 45: Integrated HSR Cohort – NYHA Class at Baseline and 1 Year
Surviving Patients with Paired Data at Baseline and 1 Year**

Baseline NYHA	1-Year NYHA				Total
	I	II	III	IV	
I	4 (66.6%)	2 (33.3%)	0 (0%)	0 (0%)	6 (2.6%)
II	18 (50.0%)	17 (47.2%)	1 (2.8%)	0 (0%)	36 (15.4%)
III	54 (36.2%)	69 (46.3%)	24 (16.1%)	2 (1.3%)	149 (63.7%)
IV	12 (27.9%)	18 (41.9%)	11 (25.6%)	2 (4.7%)	43 (18.4%)
Total	88 (37.6%)	106 (45.3%)	36 (15.4%)	4 (1.7%)	234

SF-36 Quality of Life

Table 32 shows accountability for quality of life at baseline and 1 year, noting that 254 patients are evaluable at baseline and 30 days and 191 patients are evaluable at both baseline and 1 year.

Table 46: Integrated HSR Cohort – Accountability for SF-36 at Baseline and 30 Days

Baseline SF-36	30-Day SF-36				Total
	Evaluable	Missing due to death	Missing due to other reasons	Withdrawn	
Evaluable	254	19	37	5	315
Missing	20	1	15	0	36
Total	274	20	52	5	351

Table 47: Integrated HSR Cohort – Accountability for SF-36 at Baseline and 1 Year

Baseline SF-36	1-Year SF-36				Total
	Evaluable	Missing due to death	Missing due to other reasons	Withdrawn	
Evaluable	191	75	35	14	315
Missing	20	8	7	1	36
Total	211	83	42	15	351

At baseline, patients exhibited quality of life scores, as measured by the SF-36 survey, well below population norms. Measures of physical function were markedly reduced: the physical component summary (PCS) score average was 32.7 at baseline, more than a full standard deviation below the age-adjusted (age 75+) US norm of 41.0. Smaller baseline impairments were observed in measures of mental health, with mean mental component summary (MCS) score of 44.7. Nonetheless, this is still clearly below the age-adjusted population norm of 51.4 for the MCS score¹⁹.

Improvements in components of physical score were noted at 1 year, with the exception of Bodily Pain (Figure 13). This component would not be expected to improve by MR reduction. All components of the mental score showed consistent improvement at 1 year (Figure 14).

**Table 48: Integrated HSR Cohort - Quality of Life at Baseline and Follow-up
Surviving Patients with Paired Data at Baseline and Follow-up**

Follow-up	Endpoint	Baseline	Follow-up	Difference (p-value)
30-Day	SF-36 Quality of Life, Physical Mean \pm SD (N)	32.7 \pm 8.9 (254)	38.5 \pm 9.9 (254)	5.8 \pm 9.0 (<0.0001)
	SF-36 Quality of Life, Mental Mean \pm SD (N)	44.7 \pm 13.1 (254)	48.6 \pm 12.3 (254)	4.0 \pm 12.9 (<0.0001)
1-Year	SF-36 Quality of Life, Physical Mean \pm SD (N)	34.0 \pm 9.1 (191)	38.8 \pm 11.3 (191)	4.8 \pm 10.4 (<0.0001)
	SF-36 Quality of Life, Mental Mean \pm SD (N)	44.9 \pm 13.5 (191)	49.8 \pm 12.2 (191)	5.0 \pm 13.0 (<0.0001)

Figure 13: Components of SF-36 Physical Score at Baseline and 1 Year

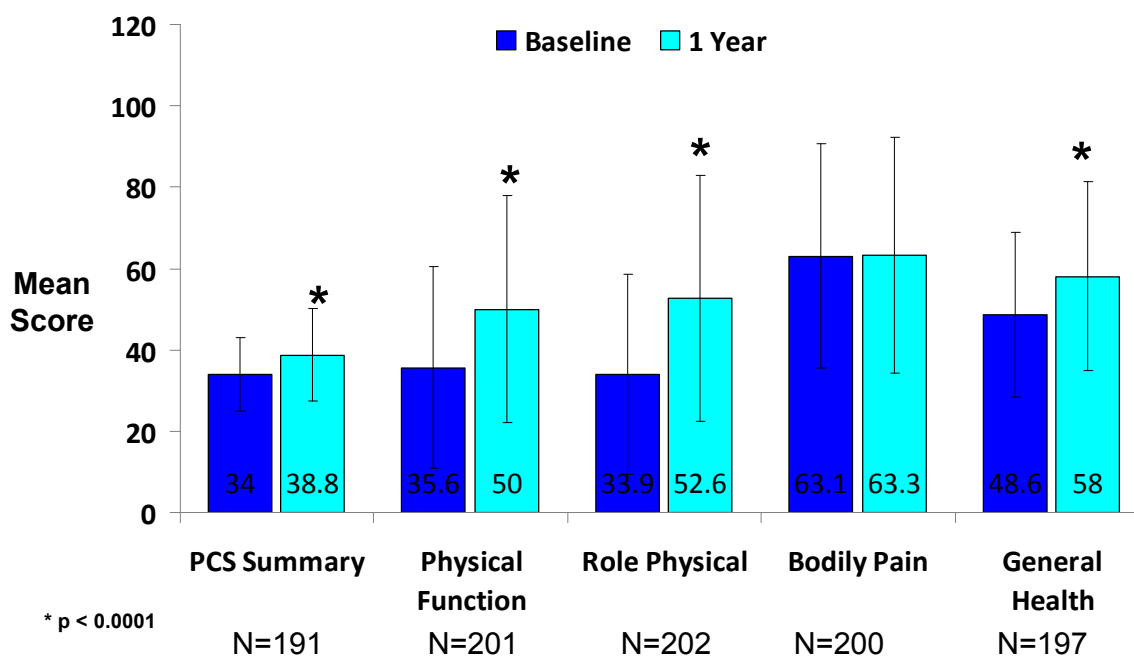
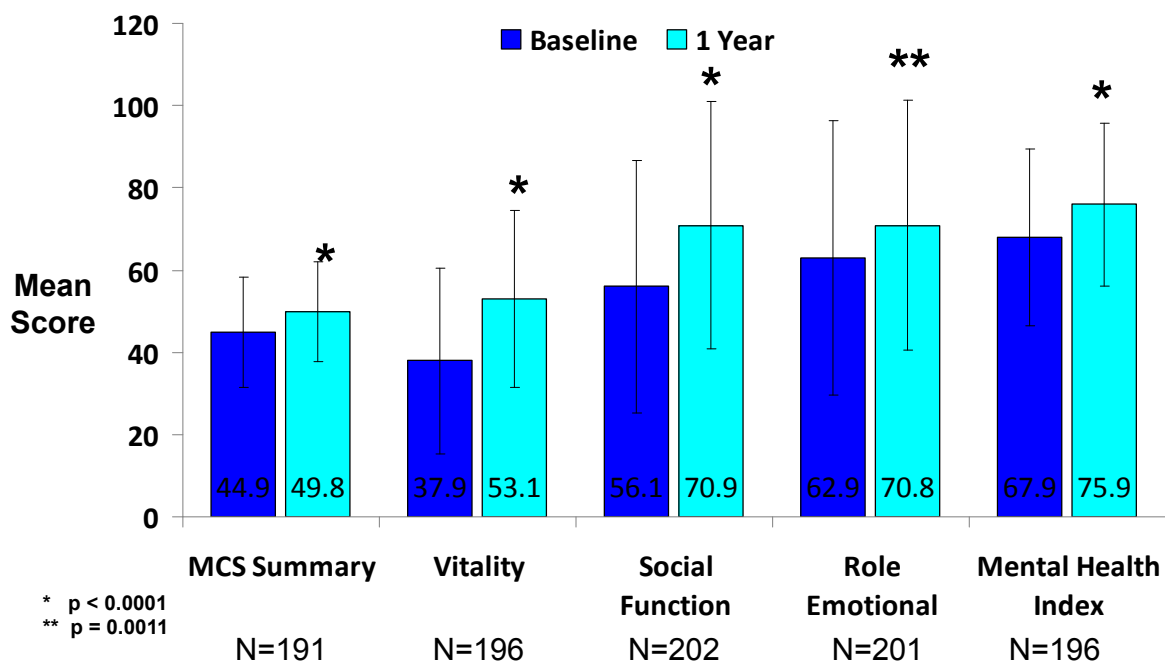


Figure 14: Components of SF-36 Mental Score at Baseline and 1 Year



Heart Failure Hospitalizations:

The heart failure hospitalization rate 1-year pre-MitraClip was compared to the rate in the 1 year follow-up period post-discharge. A Poisson regression model was used to compare the pre-baseline and post-discharge rates. Patients who died or withdrew post-discharge were included in the analysis with the length of follow-up included as an offset in the model.

A significant decrease (48%) in the rate heart failure hospitalizations (0.79 to 0.41 per patient-year) was observed in the year following the MitraClip procedure compared to the year prior (Table 49).

Table 49: Integrated HSR Cohort – Heart Failure Hospitalizations

	1-Year Pre- enrollment	Post-discharge through 1 Year	p-value
# Patients	149	67	
# Events	277	118	
Rate per patient-year of follow-up ^a (95% Two-sided Conf Int)	0.79 (0.70, 0.89)	0.41 (0.34, 0.49)	< 0.0001

^a p-value and confidence interval are obtained from a Poisson regression model

The reduction in the heart failure hospitalization rate was greater in patients with greater reductions in MR at 1 year (Table 50). There was a reduction in heart failure hospitalization rates of 54% (from 0.78 pre-enrollment to 0.36 post-discharge) in patients with reductions in MR to $\leq 2+$. However, in patients who experienced no reduction in MR, heart failure hospitalization rate remained unchanged (from 0.73 pre-enrollment to 0.74 post-discharge). Further, the reduction in the heart failure hospitalization rate was comparable between patients who experienced reduction of MR to 1+ and patients who experienced reduction of MR to 2+. These findings support the conclusion that the reduction in MR severity to 2+ or less provides significant clinical benefits.

Table 50: Integrated HSR Cohort – Heart Failure Hospitalizations by MR Severity at Discharge

HF hospitalization rate per patient-year of follow-up	Discharge MR $\leq 2+$		Discharge MR 3+/4+
1 year prior to MitraClip → 1 year post-discharge	0.78 → 0.36 (p < 0.0001)		0.73 → 0.74 (p = 0.964)
	Discharge MR $\leq 1+$	Discharge MR = 2+	
	0.66 → 0.32 (p < 0.0001)	0.92 → 0.42 (p < 0.0001)	

^a p-value obtained from a Poisson regression model

Hospitalization rates post-discharge in the above analysis may be artificially lower because patients who died during 1-year follow-up may not have experienced heart failure hospitalizations prior to death. To evaluate the effect of incomplete follow-up from deaths and withdrawals post-discharge on heart failure hospitalization rates, a sensitivity analysis was conducted, in which only patients with a year of follow-up post-discharge were included. A total of 259 patients were included in this analysis. Table 51 shows the results of this sensitivity analysis. There was a 53% reduction in heart failure hospitalization rate (from 0.77 to 0.36 per patient-year) post-discharge, consistent with the results observed in the entire cohort.

Table 51: Integrated HSR Cohort – Heart Failure Hospitalizations Patients with Incomplete Follow-up Excluded from Analysis

	1-Year Pre-enrollment	Post-discharge through 1 Year	p-value
# Patients	100	50	
# Events	184	88	
Rate per patient-year of follow-up ^a (95% Two-sided Conf Int)	0.71 (0.61, 0.82)	0.35 (0.29, 0.43)	< 0.0001

^a p-value and confidence interval are obtained from a Poisson regression model

Consistency of Clinical Benefits from MitraClip Therapy Across Studies

Measures of clinical benefit in the Integrated HSR Cohort were compared to the EVEREST II RCT, MitraClip and Surgery groups. Table 52 provides a summary of these comparisons. Clinical benefits in the Integrated HSR Cohort and the RCT MitraClip group were similar in magnitude and smaller than that obtained in the RCT Surgery group. This is consistent with the larger degree of MR reduction obtained with surgery. These results suggest that clinical benefit derived from MitraClip therapy is independent of surgical risk. Further, the consistency of the directionality in clinical benefits between MitraClip and surgery confirm the physiologic relationship between mechanical reduction of MR and its benefits. Despite the lack of a parallel comparator group for the Integrated HSR Cohort, the consistency of the results observed with the RCT provides strong evidence of the effectiveness of MitraClip therapy.

Table 52: Integrated HSR Cohort – Comparison of Effectiveness to EVEREST II RCT MitraClip and Surgery Groups

Effectiveness Measure	Integrated HSR Cohort (N = 351)	EVEREST II RCT MitraClip Group (N = 178)	EVEREST II RCT Surgery Group (N = 80)
Improvement in LVEDV at 1 year	-18 ± 32 ml	-21 ± 24 ml	-40 ± 36 ml
Improvement in LVESV at 1 year	-8 ± 23 ml	-4 ± 14 ml	-5 ± 21 ml
Improvement in SF-36 PCS score at 1 year	4.8 ± 10.4	4.7 ± 10.1	4.4 ± 10.4
Improvement in SF-36 MCS score at 1 year	5.0 ± 13.0	5.8 ± 9.7	3.8 ± 10.3
NYHA Class III or IV: Baseline → 1 year	82% → 17%	46% → 2%	46% → 12%

8.3.6.4 Integrated HSR Cohort Effectiveness Results by Patient Subgroups

8.3.6.4.1 Integrated HSR Cohort Effectiveness Results by MR Etiology

Implant success rates were high in both degenerative and functional MR subgroups (95% in DMR and 96% in FMR). Table 53 shows effectiveness outcomes by DMR and FMR. All effectiveness outcomes are based on surviving patients with paired data at baseline and 1 year, except heart failure hospitalizations, which included all patients and all available follow-up. The table shows improvements from baseline in all measures in both subgroups.

Table 53: Integrated HSR Cohort – Baseline Characteristics and Medical History and Safety Outcomes by MR Etiology

Characteristic	Degenerative MR (N = 105)	Functional MR (N = 246)
Mean Age	81.8 yrs	73.2 yrs
Patients over 75 years of age	81.0%	48.4%
Female Gender	40.0%	38.6%
Coronary Artery Disease	74.8%	85.4%
Prior Myocardial Infarction	29.5%	59.8%
Atrial Fibrillation History	71.6%	67.0%
Prior Stroke	9.5%	14.2%
Diabetes	29.5%	43.7%
Moderate to Severe Renal Disease	26.7%	32.1%
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	28.5%	29.0%
Hypertension	89.5%	89.4%
Previous Cardiovascular Surgery	50.5%	63.8%
Previous Percutaneous Coronary Intervention	35.2%	56.1%
NYHA Class III/IV Heart Failure	81.9%	86.2%
Mean LV Ejection Fraction	61.0%	41.7%
Mean LV Internal Diameter systole	3.4 cm	4.7 cm
Effectiveness Measure	Degenerative MR (N = 105)	Functional MR (N = 246)
Implant Success	95%	96%
MR ≤ 1+ at discharge	49%	45%
MR ≤ 2+ at discharge	81%	88%
MR ≤ 1+ at 1 year	31%	40%
MR ≤ 2+ at 1 year	85%	83%
Improvement in LVEDV at 1 year	19 ml	18 ml
Improvement in LVESV at 1 year	4 ml	10 ml
Improvement in SF-36 PCS at 1 year	6.4	4.1
Improvement in SF-36 MCS at 1 year	4.3	5.3
NYHA Class III or IV: Baseline → 1 year	79% → 13%	83% → 19%
Rate of hospitalizations for heart failure	0.70 → 0.20	0.83 → 0.50

8.3.6.4.2 Integrated High Surgical Risk Cohort Effectiveness Results by Sex

Implant success rates were high in both groups of patients (96% in males and females respectively).

Table 54 shows effectiveness outcomes by males and females. All effectiveness outcomes are based on surviving patients with paired data at baseline and 1 year, except heart failure hospitalizations, which included all patients and all available follow-up. The table shows improvements from baseline in all measures in both subgroups.

Table 54: Integrated HSR Cohort – Baseline Characteristics and Medical History and Safety Outcomes by Sex

Characteristic	Male (N = 214)	Female (N = 137)
Mean Age	76.5 yrs	74.6 yrs
Patients over 75 years of age	60.7%	54.0%
Coronary Artery Disease	89.3%	71.1%
Prior Myocardial Infarction	56.6%	41.6%
Atrial Fibrillation History	72.0%	62.9%
Prior Stroke	12.6%	13.1%
Diabetes	36.9%	43.4%
Moderate to Severe Renal Disease	33.2%	26.3%
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	29.0%	28.7%
Hypertension	88.3%	91.2%
Previous Cardiovascular Surgery	69.6%	44.5%
Previous Percutaneous Coronary Intervention	51.9%	46.7%
NYHA Class III/IV Heart Failure	81.8%	89.8%
Mean LV Ejection Fraction	46.4%	49.1%
Mean LV Internal Diameter systole	4.6 cm	4.0 cm
Effectiveness Measure	Male (N = 214)	Female (N = 137)
Implant Success	96%	96%
MR ≤ 1+ at discharge	50%	41%
MR ≤ 2+ at discharge	87%	83%
MR ≤ 1+ at 1 year	35%	39%
MR ≤ 2+ at 1 year	82%	87%
Improvement in LVEDV at 1 year	18 ml	18 ml
Improvement in LVESV at 1 year	7 ml	9 ml
Improvement in SF-36 PCS at 1 year	4.4	5.5
Improvement in SF-36 MCS at 1 year	5.4	4.4
NYHA Class III or IV: Baseline → 1 year	79% → 20%	87% → 13%
Heart failure hospitalization rate	0.60 → 0.41	1.09 → 0.41

8.3.6.4.3 Integrated HSR Cohort Effectiveness Results by STS Risk $\geq 12\%$ and $< 12\%$

Implant success rates were high in both groups of patients (96% in males and females respectively). Table 55 shows effectiveness outcomes by STS risk $\geq 12\%$ vs $< 12\%$. All effectiveness outcomes are based on surviving patients with paired data at baseline and 1 year, except heart failure hospitalizations, which included all patients and all available follow-up. The table shows improvements from baseline in all measures in both subgroups.

Table 55: Integrated HSR Cohort – Baseline Characteristics and Medical History by STS risk $\geq 12\%$ and $< 12\%$

Characteristic	STS $\geq 12\%$ (N = 151)	STS $< 12\%$ (N = 200)
Mean Age	81.1 yrs	71.7 yrs
Patients over 75 years of age	76.8%	44.0%
Female Gender	46.4%	33.5%
Coronary Artery Disease	81.2%	83.0%
Prior Myocardial Infarction	50.0%	51.3%
Atrial Fibrillation History	75.9%	62.8%
Prior Stroke	13.9%	12.0%
Diabetes	45.3%	35.0%
Moderate to Severe Renal Disease	47.7%	17.5%
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	31.7%	26.6%
Hypertension	95.4%	85.0%
Previous Cardiovascular Surgery	51.7%	66.0%
Previous Percutaneous Coronary Intervention	49.7%	50.0%
NYHA Class III/IV Heart Failure	92.7%	79.0%
Mean LV Ejection Fraction	50.1%	45.3%
Mean LV Internal Diameter systole	4.0 cm	4.6 cm
Effectiveness Measure	STS $\geq 12\%$ (N = 151)	STS $< 12\%$ (N = 200)
Implant Success	94.7%	96.5%
MR $\leq 1+$ at discharge	47.9%	44.8%
MR $\leq 2+$ at discharge	83.1%	88.0%
MR $\leq 1+$ at 1 year	37.7%	36.4%
MR $\leq 2+$ at 1 year	82.9%	84.1%
Improvement in LVEDV at 1 year	-19.3 ml	-16.9 ml
Improvement in LVESV at 1 year	-7.6 ml	-8.4 ml
Improvement in SF-36 PCS at 1 year	3.5	5.7
Improvement in SF-36 MCS at 1 year	5.4	4.7
NYHA Class III or IV: Baseline \rightarrow 1 year	92.5% \rightarrow 20.5%	75.1% \rightarrow 14.9%
Heart failure hospitalization rate	1.06 \rightarrow 0.52	0.59 \rightarrow 0.34

8.3.6.5 Durability in the Integrated HSR Cohort Through 3 Years

Freedom from MR > 2+ and freedom from MR > 1+ in surviving patients through 3 years are shown in Table 56. MR reduction to $\leq 2+$ is durable in a majority of patients ($\geq 83\%$) through 3 years and MR is $\leq 1+$ in greater than one-third of patients through 3 years. Reduction in left ventricular volumes and improvement in NYHA Class are also sustained through 3 years, as shown in Table 57 and Table 58.

Table 56: Integrated HSR Cohort – Durability of MR Reduction

Durability of MR Reduction	Follow-up	N	Proportion of Patients
Freedom from MR > 2+	1-Year	225	83.6%
	2-Year	109	87.2%
	3-Year	37	86.4%
Freedom from MR > 1+	1-Year	225	36.9%
	2-Year	109	45.0%
	3-Year	37	43.2%

Table 57: Integrated HSR Cohort – Durability of Reduction in Left Ventricular Size Patients with Paired Data at Baseline and Follow-up

LV Measurement	Follow-up	N	Difference (Follow-up - Baseline)	p-value
LVEDV, ml				
Mean \pm SD	1-Year	203	-17.9 \pm 31.8	<0.001
	2-Year	97	-31.2 \pm 38.8	<0.001
	3-Year	36	-39.5 \pm 38.1	<0.001
LVIDd, cm				
Mean \pm SD	1-Year	221	-0.2 \pm 0.4	<0.001
	2-Year	97	-0.4 \pm 0.5	<0.001
	3-Year	37	-0.3 \pm 0.6	0.001
LVESV, ml				
Mean \pm SD	1-Year	202	-8.1 \pm 23.2	<0.001
	2-Year	105	-12.1 \pm 29.5	<0.001
	3-Year	36	-14.9 \pm 25.5	0.001
LVIDs, cm				
Mean \pm SD	1-Year	210	-0.1 \pm 0.6	0.002
	2-Year	99	-0.1 \pm 0.6	0.038
	3-Year	37	0.0 \pm 0.7	0.584

Table 58: Integrated HSR Cohort – Durability of Improvement in NYHA Class Patients with Paired Data at Baseline and Follow-up

	Follow-up	N	Proportion of Patients
Freedom from NYHA Class III or IV	Baseline \rightarrow 1-Year	234	17.9% \rightarrow 82.9%
	Baseline \rightarrow 2-Year	111	18.0% \rightarrow 84.7%
	Baseline \rightarrow 3-Year	37	13.5% \rightarrow 81.1%

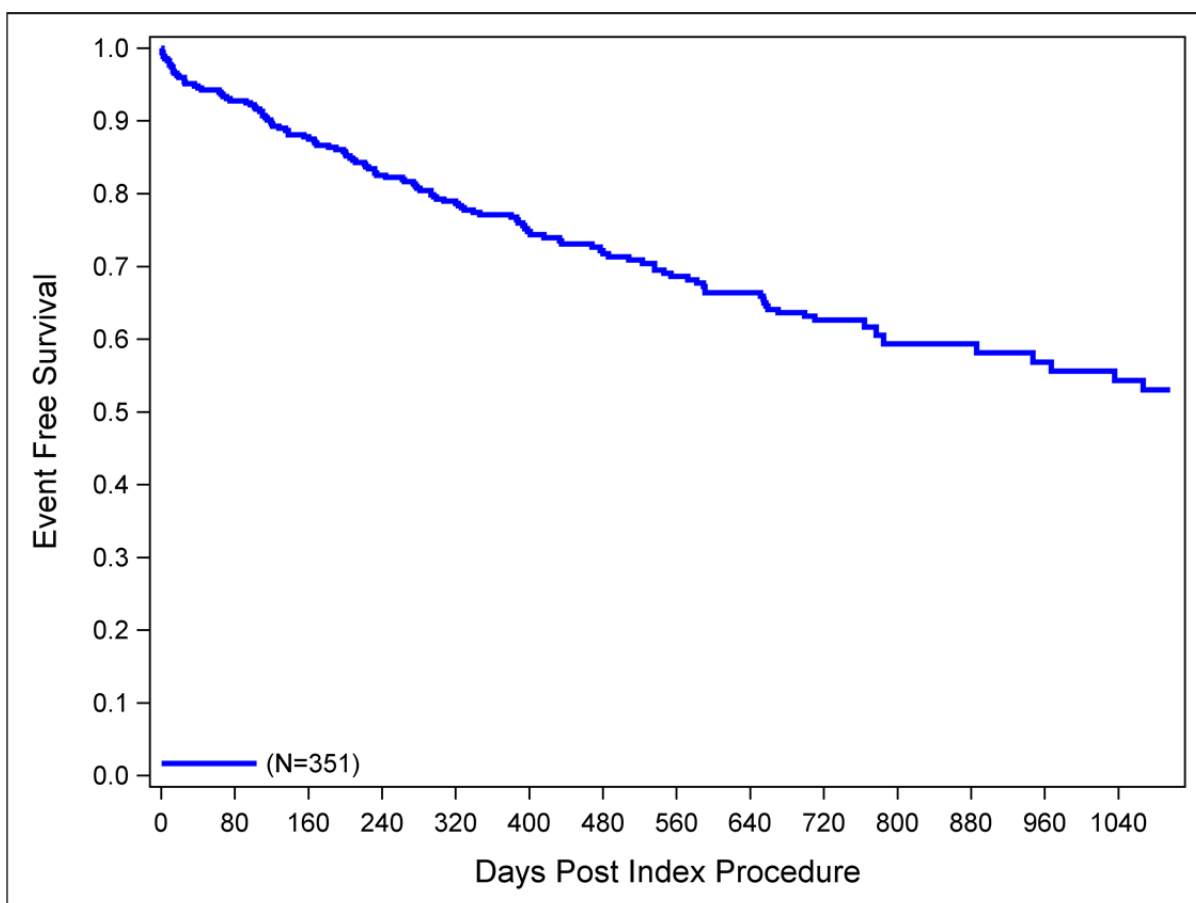
A low rate of mitral valve surgery has occurred in the Integrated HSR Cohort. At 1 year, freedom from mitral valve surgery was high, at 97.8%. In a majority of patients who underwent mitral valve surgery, the reason for the surgery was due to technical failure to place the MitraClip Device or recurrent MR due to SLDA or progression of disease rather than due to safety reasons. Freedom from mitral valve surgery remained high (96.1%) at 2 years.

8.3.6.6 Survival in the Integrated High Surgical Risk Cohort through 3 Years

The Kaplan-Meier estimate of survival in the Integrated HSR Cohort at 1 year was 77.1%. As discussed earlier, the Duke analysis showed that there was at most a hazard ratio of 1.08 for mortality in MitraClip patients versus Duke patients who were managed non-surgically. This represents a tolerable mortality risk for the high surgical risk population with limited treatment options for MR reduction.

Survival at 2 years and 3 years was 62.7% and 53.1% respectively (see Figure 15).

Figure 15: Integrated HSR Cohort - Kaplan-Meier Survival Through 3 Years



Time Post Index Procedure	Baseline	30-Day	1-Year	2-Year	3-Year
# At Risk	351	329	229	99	40
# Censored	1	5	46	141	192
# Events	0	17	78	111	119
% Event Free	100%	95.1%	77.1%	62.7%	53.1%
95% CI	-	[92.2%, 96.9%]	[71.9%, 81.5%]	[54.6%, 69.7%]	[41.2%, 63.5%]

9.0 Procedural Experience and Safety Across Development

9.1 Procedure Duration

Procedure time, the time from the transseptal procedure to the time the Steerable Guide Catheter is removed, and device time, from insertion of the Steerable Guide Catheter to the time the MitraClip Delivery Catheter is retracted, both decreased over the course of the clinical development program. There was a 108 minute decrease in average procedure time, 86 minute decrease in average device time, and a 20 minute decrease in average fluoroscopy time from EVEREST I to REALISM HR.

Table 59: Procedure Duration by Study

Endpoint	EVEREST I	EVEREST II RCT	EVEREST II HRR	REALISM Surgical Arm	REALISM HR Arm
Procedure Time (min)					
Mean ± SD (N)	255 ± 105 (55)	188±76 (174)	190±80 (77)	153 ±76 (126)	147 ±66 (268)
Device Time (min)					
Mean ± SD (N)	199 ± 99 (55)	146±70 (170)	145±75 (78)	127 ±72 (127)	113 ±59 (269)
Contrast Volume (ml)					
Mean ± SD (N)	112 ± 55 (54)	67±59 (171)	35±42 (77)	NC	NC
Fluoroscopy Duration (min)					
Mean ± SD (N)	60 ± 31 (54)	51±30 (175)	53±29 (77)	38 ±22 (132)	40 ±22 (272)

NC: Not Collected

9.2 Number of MitraClip Devices Implanted

MitraClip implant rates improved over the course of time between the EVEREST I and REALISM studies (2005 through 2011) (**Table 60**) with 93% of surgical candidate patients and 96% of high surgical risk patients being implanted in REALISM. Physicians had the option of deploying 2 MitraClip devices if a single Device did not provide satisfactory MR reduction and the mitral valve area was large enough to allow a second MitraClip device to be placed without resulting in mitral stenosis. The use of 2 MitraClip devices remained stable over the course of time (2005 through 2011) between the EVEREST II and REALISM studies.

Table 60: Number of MitraClip Devices Implanted - US MitraClip Trials

Number of MitraClips Implanted	EVEREST I	EVEREST II RCT	EVEREST II HRR	REALISM Surgical Arm	REALISM HR Arm
0	10.9%	11.2%	3.8%	6.8%	4.4%
1	61.8%	50.6%	59.0%	56.8%	56.8%
2	27.3%	38.2%	37.2%	36.4%	38.8%

9.3 Post-Procedure ICU/CCU/PACU Duration

Post-procedure length of hospital stay is defined as the number of days from the end of the procedure until the patient is discharged from the hospital. This does not include time in a nursing home or skilled nursing facility. The mean post-procedure ICU length of stay has decreased substantially over the course of time (2005-2011) between the EVEREST and REALISM studies for both surgical candidate and high surgical risk patients (Table 61). These results were obtained despite the fact that the REALISM study, particularly the surgical candidate arm, enrolled patients with a higher rate of baseline co-morbidities than the EVEREST II studies. The short recovery period observed is especially important in a high surgical risk elderly population who would otherwise be hospitalized for longer durations after surgery.

Table 61: Post-Procedure ICU/CCU/PACU Duration - US MitraClip Trials

Endpoint	EVEREST I	EVEREST II RCT	EVEREST II HRR	REALISM Surgical Arm	REALISM HR Arm
Post-procedure ICU/CCU/PACU duration (hours)	56.7 ± 80.2	38.6 ± 135.9	52.3±80.6	20.7 ±30.2	32.7 ±53.0
Post-procedure hospital stay (days)	3.0 ± 3.5	2.6 ±6.3	3.9±6.4	2.5 ±3.7	3.0 ±4.4

9.4 Discharge Facility

The majority of both high surgical risk and surgical candidate patients across the EVEREST II and REALISM studies were discharged home without home healthcare (Table 62). There was a slight increase in the proportion of surgical candidate patients in REALISM who were discharged home with health care, which may be explained by the higher rate of baseline co-morbidities in REALISM surgical candidate patients compared to patients in the EVEREST II RCT. Between the REALISM HR and the EVEREST II HRR studies, there were reductions in the proportions of patient discharged to long term acute care and to a nursing home or skilled nursing facility or hospital.

Table 62: Post-Procedure Discharge Facility - US MitraClip Trials

Endpoint	EVEREST I	EVEREST II RCT	EVEREST II HRR	REALISM Surgical Arm	REALISM HR Arm
Discharged home without home healthcare	NC	94.9%	75.6%	91.5%	87.5%
Discharged home with home healthcare		1.1%	10.3%	4.8%	5.9%
Discharged to nursing home / skilled nursing facility/hospital		3.4%	7.7%	2.2%	4.4%
Long-term acute care		0.0%	2.6%	0.4%	0.0%
Expired before discharge		0.6%	3.8%	0.7%	2.2%

NC: Not Collected

9.5 Association of MR Reduction with Clinical Benefit

Analyses of change between baseline and 12 months presented in the sections above only include matched cases. MR severity and objective echocardiographic measures of effectiveness including LVEDV and LVESV were obtained longitudinally at baseline and follow-up (discharge, 30 days, 6 months and 12 months). NYHA Functional Class was also collected longitudinally at baseline and follow-up. An assessment of the association of MR reduction with clinical benefit was therefore performed using data available over all follow-up through 12 months using statistical methods for longitudinal data analyses.

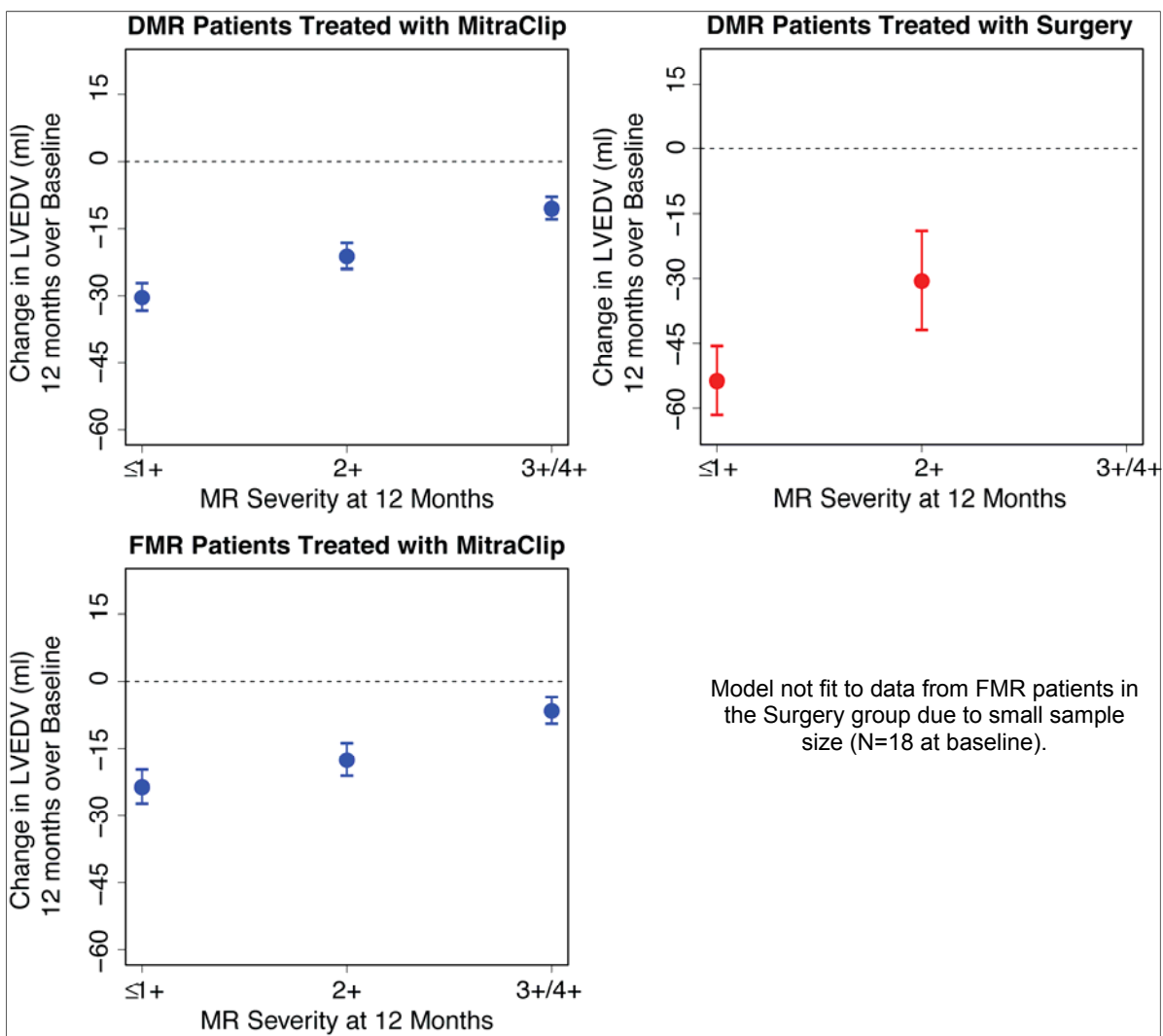
The continuous measures (LVEDV and LVESV) were analyzed using mixed effect models which incorporated repeated observations from patients. Data from the EVEREST II RCT (N = 178 Device, N = 80 Surgery), EVEREST II HRR (N = 78) and REALISM studies (N = 272 Surgical Candidates, N = 273 High Surgical Risk) were included in the models. Separate models by MR etiology were fit to each measure of effectiveness. The models included MR severity ($\leq 1+$, $2+$, $3+/4+$) as a fixed effect, time as a continuous covariate and patient as a random effect. The models thus accounted for the correlation within patient over time. The models were then used to estimate the changes in LVEDV and LVESV associated with changes in MR severity between baseline and 12 months. Similar models were also fit to the data for DMR patients from the Surgery group of the EVEREST II RCT to evaluate consistency of the associations between MR reduction and clinical benefit. The models were not fit to data from FMR patients in the Surgery group due to small sample size (N=18 at baseline).

NYHA Functional Class III/IV (Yes/No) was analyzed using nominal logistic regression with Generalized Estimating Equations (GEE). Data from the EVEREST II RCT, EVEREST II HRR and REALISM studies were included in the models. Separate models by MR etiology and surgical risk status were fit to the data. An AR(1) working correlation matrix was assumed to account for correlation within patient. The models included the effect of MR severity ($\leq 1+$, $2+$, $3+/4+$), surgical risk status and time as a continuous covariate. The models were then used to derive the predicted probability of NYHA Class III/IV symptoms at baseline, and at 12 months for various levels of MR severity.

- **LVEDV**

MR severity was significantly associated with LVEDV ($p < 0.0001$ for both FMR and DMR) in patients treated with the MitraClip device. MR severity was also significantly associated with LVEDV in DMR patients treated with Surgery ($p < 0.0001$). In both DMR and FMR patients treated with the MitraClip device, reduction of MR severity to $\leq 2+$ at 12 months was associated with significant decreases of LVEDV (Figure 16). As expected, since surgery achieves greater reduction of MR, the corresponding decrease in LVEDV in DMR patients treated with surgery was larger.

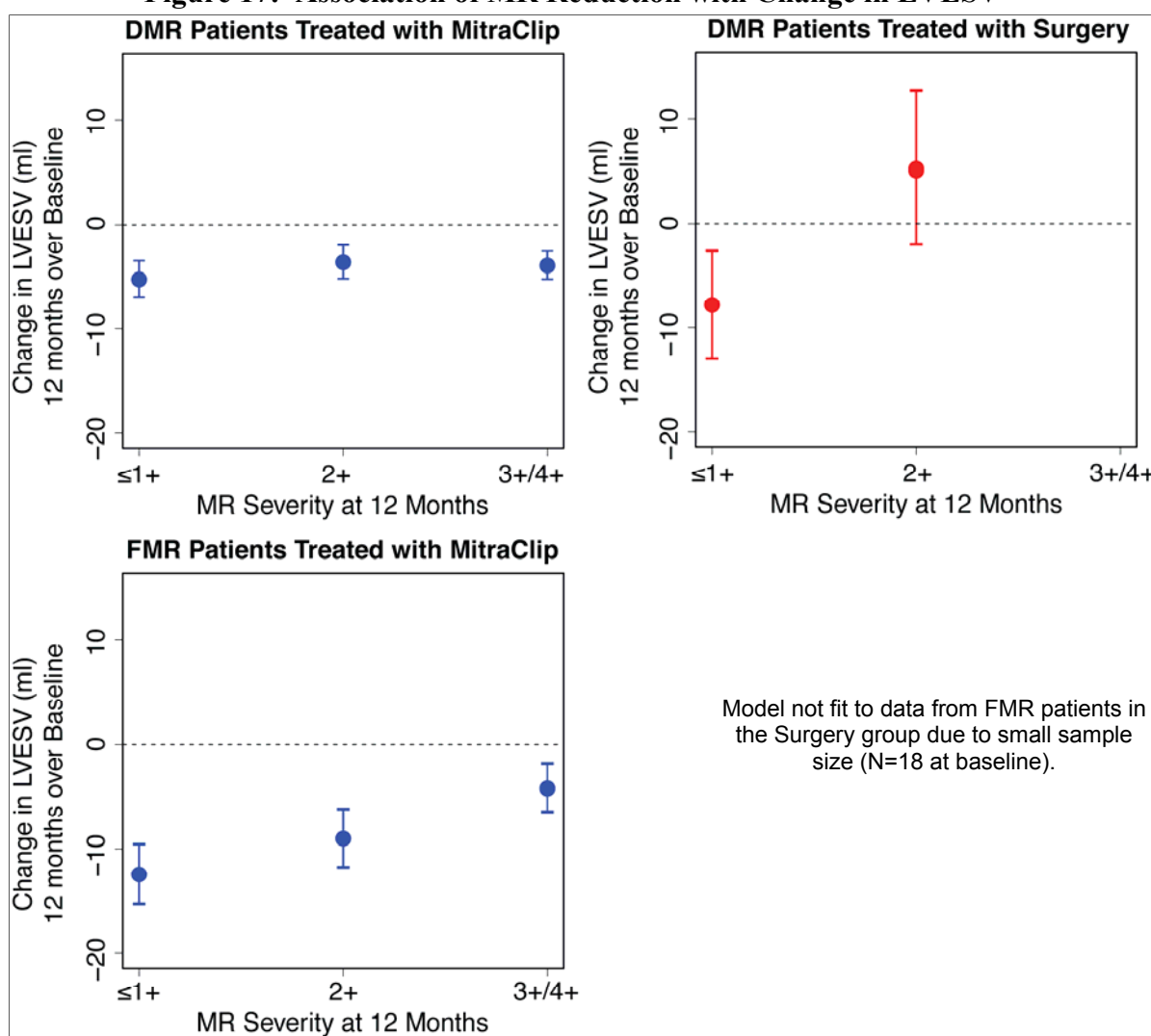
**Figure 16: Association of MR Reduction with Change in LVEDV
12 Months over Baseline**



- **LVESV**

MR severity was not significantly associated with LVESV ($p=0.069$) in DMR patients treated with the MitraClip device. MR severity was however significantly associated with LVESV ($p<0.0001$) in FMR patients treated with the MitraClip device. MR severity was also significantly associated with LVESV in DMR patients treated with surgery ($p<0.0005$). In FMR patients treated with the MitraClip device, reduction of MR severity to $\leq 2+$ resulted in significant decreases of LVESV (Figure 17).

Figure 17: Association of MR Reduction with Change in LVESV

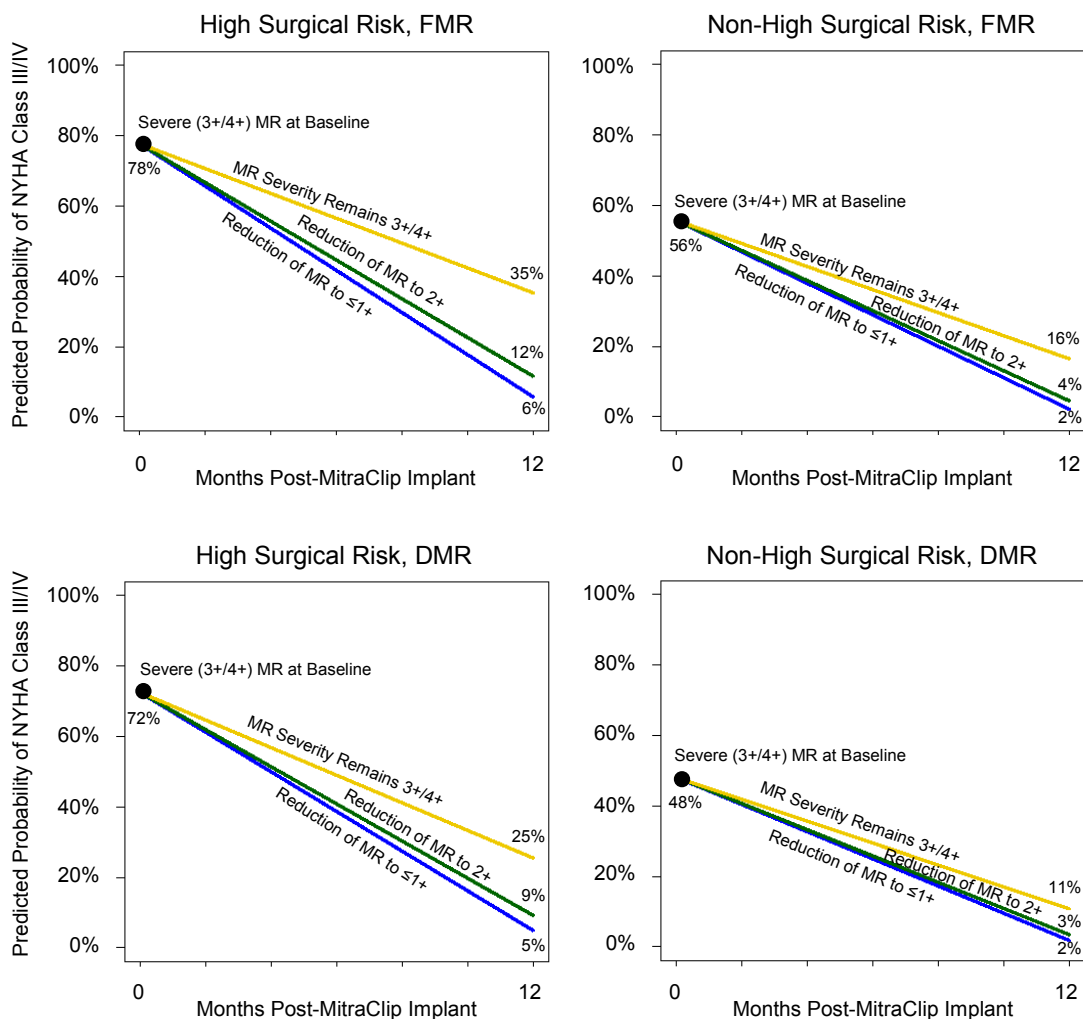


- NYHA FUNCTIONAL CLASS**

MR severity was significantly associated with the presence of NYHA Class III/IV symptoms in patients treated with the MitraClip device ($p < 0.0001$ for both FMR and DMR). Figure 18 shows the predicted probability of NYHA Functional Class III/IV at a baseline MR severity of 3+/4+ and the decrease in this probability at 12 months in FMR patients. Analogous results for DMR patients are also presented.

As expected, high surgical risk patients were more likely to experience NYHA Class III/IV symptoms at baseline than surgical candidate patients. In FMR patients, although there was a decrease in the probability of NYHA Class III/IV even in patients whose MR severity remained 3+/4+ at 12 months, this decrease was much smaller than in patients with MR reduced to $\leq 2+$. Similar results were also obtained in DMR patients.

Figure 18: Association of MR Reduction with Presence of NYHA Class III/IV Symptoms in MitraClip Patients - 12 Months over Baseline



In summary, the consistency of the association of MR reduction with improvements in objective echocardiographic measures between patients treated with the MitraClip device or surgery establishes the biological plausibility of the benefits observed in MitraClip patients. The low likelihood of NYHA Class III/IV symptoms at 12 months observed with improvement in MR to $\leq 2+$ is unlikely to be a placebo effect. Patients whose MR severity improved to $\leq 2+$ at 12 months were much less likely to be experiencing NYHA Class III/IV symptoms than patients with no improvement in MR. In conclusion:

- reduction of MR with the MitraClip was associated with significant clinical benefit in both objective and subjective measures
- reduction of MR to 2+ conferred significant clinical benefit

Table 63: Summary of Key Safety and Effectiveness Data from US Clinical Trials
(N = 916 MitraClip, N = 80 Surgery)

	Endpoint	Surgical Candidates			High Surgical Risk		
		EII RCT	REALISM	Surgery	EII HRR	REALISM	Integrated HR Cohort
Safety	30-Day MAE Rate	14.6%	11.4%	56.3%	26.9%	16.5%	18.8%
	30-Day MAE Rate (excluding Transfusions ≥ 2 units)	4.5%	7.0%	11.3%	12.8%	8.1%	9.1%
	30-Day Mortality Rate	1.1%	1.5%	2.5%	7.7%	4.0%	4.8%
	12-Month MAE Rate	32.6%	26.5% ^a	61.3%	42.3%	36.6%	22.8%
	12-Month MAE Rate (excluding Transfusions ≥ 2 units)	15.7%	17.3% ^a	17.5%	30.8%	27.8%	27.9%
	Freedom from 12-Month Mortality	93.7%	91.0%	92.3%	75.6%	77.7%	77.2%
	Freedom from 24-Month Mortality	90.0%	85.1%	89.6%	64.6%	63.3%	63.8%
Effectiveness Objective Measures	Change: 12 Months over Baseline						
	MR Severity 3+/4+ Rate Difference	-77.2%	-73.9%	90.9%	-75.9%	-67.2%	-68.7%
	MR Severity 2+/3+/4+ Rate Difference	-39.0%	-33.5%	-77.3%	-31.5%	-38.0%	-36.5%
	LVEDV Mean Change ± SD	-21.3±24.1	-11.9±22.5	-40.2±36.2	-32.1±28.1	-12.7 ±31.6	-17.9 ±31.8
	LVESV Mean Change ± SD	-4.4±14.0	-2.2 ±11.0	-5.1±20.8	-10.0±21.5	-7.3 ±23.8	-8.1 ±23.2
	Reduction in CHF Hospitalization Rate	NA	NA	NA	45%	48%	48%
Effectiveness Subjective Measures	12 Months over Baseline						
	NYHA Class III/IV Rate Difference	-45.2%	-42.7%	-24.2%	-63%	-65.6%	-65.0%
	SF-36 PCS Mean Change ± SD	4.7±10.1	6.3±9.7	4.4±10.4	4.0±10.6	5.1±10.4	4.8 ±10.4
	SF-36 MCS Mean Change ± SD	5.8±9.7	2.1±11.2	3.8±10.3	3.2±11.7	5.5±13.3	5.0 ±13.0
Durability to 24 Months	Freedom from MV Surgery	78.2%	88.2%	96.0%	95.1%	93.5%	95.2%
	Freedom from Death and MV Surgery	71.0%	76.8%	87.0%	63.2%	58.7%	60.3%
	Freedom from Death, MV Surgery and MR>2+	56.8%	67.0%	82.8%	53.3%	51.7%	52.9%
	Freedom from Death, MV Surgery and MR>1+	25.8%	26.6%	70.7%	30.5%	32.0%	29.2%

^a 6 REALISM surgical candidate patients are pending MAE adjudication through 12 months

9.6 Special Safety Topics

9.6.1 Single Leaflet Device Attachment

Single Leaflet Device Attachment (SLDA) refers to the circumstance when the MitraClip device remains attached to only one leaflet rather than coapting both leaflets of the mitral valve. The rate of SLDA decreased markedly over the course of the clinical development program is shown in (Table 64).

Table 64: SLDA Rate by Study

SLDA Rate	EVEREST I	EVEREST II Roll-In	EVEREST II RCT	EVEREST II HRR	REALISM Surgical Arm	REALISM HR Arm
	10.2%	10.9%	6.3%	1.3%	4.2%	2.7%

One patient (1.3%, 1/ 75) implanted with a MitraClip device experienced an SLDA through 1 year in the EVEREST II HRR cohort. This patient had a successful second intervention to place a MitraClip device with MR reduced to 2+. In REALISM HR, 7 SLDAs were reported. Three patients () underwent a second intervention to place an additional MitraClip device, 3 patients () underwent mitral valve surgery and 1 patient () died 7 days post-index procedure.

9.6.2 Device Embolization

No MitraClip embolizations were reported in the 1483 (916 US + 567 ACCESS-EU Phase I) patients. There have been a total of 2 MitraClip embolization cases reported out of >11,000 devices implanted worldwide (<0.02%). One case in 2010 reported an SLDA with refractory MR successfully treated by MV surgery. During surgery the Clip was not noted on the valve and detected in the right renal artery under fluoro. The Clip was left in place with no known clinical sequelae. The second case occurred in 2012, in which the Clip was visualized on discharge echo in the papillary muscle and retrieved using percutaneous methods.

In April 2011, the MitraClip Clip Delivery System underwent a voluntary global Field Safety Corrective Action due to three (3) incidences of Radiopaque Ring detachment from the Delivery Catheter. Two of the events occurred in Europe and resulted in surgical intervention and the third in the US was resolved percutaneously during the procedure. The issue was resolved through design enhancements for component attachment to the Delivery Catheter and approved by FDA via IDEG030064/S203 in August 2011.

9.6.3 Mitral Valve Stenosis

Table 65 shows mitral valve stenosis rates during the course of the clinical development program. The rate of mitral valve stenosis was low and stable over time.

Table 65: Mitral Stenosis by Study

	EVEREST I	EVEREST II RCT	EVEREST II HRR	REALISM Surgical Arm	REALISM HR Arm
Mitral Valve Stenosis Rate	2.0%	1.9%	2.7%	1.2%	0.4%

10.0 Post Approval Commitments

10.1 Abbott Vascular Commitment to Responsible Commercialization

The MitraClip was commercially launched in Europe in September 2008. Globally, there are approximately 230 heart centers implanting the MitraClip device and over 8,000 patients have been treated. Each of the 230 heart centers has completed the Abbott Vascular MitraClip training program. Abbott Vascular's focus is to ensure excellent patient outcomes by:

- Determining the most appropriate treatment centers
- Delivering robust training
- Responsible controlled roll-out of the MitraClip therapy
- Implementing a Post Approval Study in conjunction with the TVT registry

The key to commercialization efforts is Abbott's commitment to responsible dispersion and excellence in training. In each heart center, the existence of a heart team comprised of a cardiac surgeon, an implanting physician (if it is not the cardiac surgeon) and an echocardiographer is required. All specialities are required to assess patient appropriateness for each procedure. Abbott has declined to commercialize in centers where all specialities are not available.

All sites must have the following criteria:

- Multi-disciplinary heart team
- Mitral valve surgery experience
- Infrastructure for imaging and sterile environment
- Commitment to an active program and maintenance of skills

In addition, Abbott Vascular takes into account PCI volume, mitral valve surgery volume, transeptal experience, TAVR experience, presence of a valve clinic and facilities when identifying appropriate treatment centers.

Abbott Vascular plans to implement a highly disciplined rollout of this technology. Although there are over 2000 interventional centers and 1200 cardiac surgery programs in the United States, only up to 150 centers will be trained in the first year of commercialization. The pace will be dependent on maintaining high procedural outcomes.

10.2 US Physician Training

Abbott Vascular is committed to train physicians and clinicians in the safe and effective use of the MitraClip device as a therapeutic option for patients deemed too high risk for surgery, consistent with the product labeling. The heart team approach and pre-procedural screening are critical in determining patient appropriateness for the MitraClip. Abbott Vascular has developed detailed training materials for the heart team with a focus on the MitraClip System, patient screening, patient selection, and procedure training for the heart team.

The Abbott training program is a multi-faceted course including:

- Foundational didactic course
- Simulation training
- Patient screening protocol
- Device preparation and use
- Case observation
- Proctoring and on-going support by Abbott Vascular certified proctors

After site selection and prior to training, the heart team requirements will be reviewed at an initial meeting. Sites are then provided with the training manual along with recommended echocardiographic views to establish a systematic approach for patient selection and treatment. The training materials provide extensive information on patient screening to ensure that suitable candidates for the MitraClip are identified per product labeling. Patient screening includes evaluation of patient MR severity, surgical risk status, and mitral valve anatomy.

The heart team begins with a step-by-step program to guide site start up and development. Patient screening is an extremely important process and a site is trained on obtaining the necessary TTE and TEE views. All members of the heart team are required to attend a formal training course. In addition, pre-procedural consultation and decision making processes are addressed. Abbott Vascular trains the heart team on the MitraClip device, not only the function of each portion of the system but the design intent and why the physicians need to operate the system in a specific manner. The heart team is trained on device preparation and proper handling.

The Training materials include sections on pre-procedure MitraClip Device Preparation, procedure and techniques (e.g., room set up, ancillary equipment needed, anesthesia, patient preparation, echo cardiogram review and assessment, transseptal location and step by step explanation of the MitraClip procedure using both echocardiography and fluoroscopy). This is followed by instructions on evaluating the mitral regurgitation after the clip has been

implanted yet not deployed, deployment of the MitraClip, post MitraClip implantation, delivery system and guiding catheter removal and closure of the puncture site. The training materials provide multiple peri-procedure considerations before the MitraClip is fully deployed.

The Training materials also include an optional simulation program tool called the MitraClip Virtual Procedure (MVP) which provides an additional means for the operator to practice the procedural steps and to show the heart team the relative positions of the MitraClip simultaneously in both a fluoroscopy and echocardiography views. The simulation program runs on a standard laptop whereby the heart team can virtually manipulate the MitraClip System components, the echo probe and see the relative positions of MitraClip in a 3-dimensional view of the heart, a 2-dimensional view on echocardiogram and a fluoroscopy view.

The heart team will go through skills assessment which will be signed off by a certified Abbott Vascular Proctor. These assessments include patient preparation, system preparation, procedural steps, system deployment and system removal. After the didactic and skills assessment portion of the training, the heart team is ready to perform their first case. Each site is proctored by an Abbott Vascular certified proctor who has gone through an extensive training program and has participated in numerous MitraClip procedures.

The proctor is required to support MitraClip procedures until the heart team is deemed ready for independence, but not less than 10 cases in the presence of a certified proctor. After the site is fully independent, the Abbott Vascular representative will attend cases as needed. If the site has not completed a procedure within the prior 6 months, an Abbott Vascular proctor will re-train the site and perform a skills assessment.

The Training program has been developed and refined over the last 5 years. Over 700 physicians have been trained globally and over 7800 cases have been proctored. A very high procedure success rate of over 95% has been sustained as showed in the REALISM Continued Access Study in the US and ACCESS registry in Europe.

10.3 Proposed Post Approval Clinical Program

Abbott Vascular is committed to a comprehensive post-approval clinical program consisting of four main cornerstones:

- 5-year follow-up on all patients enrolled in US IDE studies
- Entry of all post-approval patients into a National MitraClip Registry
- Rapid initiation of a Post-Approval Study

10.3.1 Long-Term Follow-up to 5-years

Abbott Vascular is committed to ensuring that 5-year follow-up is collected and analyzed for all patients enrolled in the pre-approval studies. This includes over 900 patients from across the randomized EVEREST II RCT and patients from the single-arm EVEREST II HRR and REALISM Continued Access studies. This important patient follow-up will allow analysis and reporting of long-term outcomes with the MitraClip to FDA and in the medical literature.

10.3.2 National MitraClip Registry

Abbott Vascular has been working in active partnership with both ACC and STS to ensure that all commercial patients in the United States will be enrolled in a National MitraClip Registry as part of the Transcatheter Valve Therapy (TVT) registry. Extensive work has already been completed to ensure the availability of data capture at commercial sites immediately upon approval of the MitraClip therapy. Abbott Vascular is committed to the success of this program. The continued collection of registry data will allow for ongoing monitoring of clinical outcomes data. Additionally, a large established registry such as this provides for individualized data reporting on the use of the device in the real-world setting, and thus permits outcomes to be analyzed and reported by site.

10.3.3 Post Approval Study

Abbott Vascular is working in conjunction with FDA to design a Post Approval Study nested within the TVT Registry which will be launched when the MitraClip is approved for commercial use. The post approval study will first confirm the safety and effectiveness of the MitraClip in a commercial setting. Additionally, the study will confirm that the device can be used safely by implanting physicians with varying degrees of experience and identify any low-frequency or unanticipated MitraClip device related events that may occur.

Full details of the post approval study will be defined in collaboration with the FDA once final labeling for the MitraClip has been completed. The Post Approval Study is expected to be a prospective, single-arm, multicenter study of approximately 2400 patients enrolled in accordance with the labeled indication. Patients will be stratified equally between Functional (FMR) and degenerative (DMR) etiologies. All patients in the Post Approval Study will have follow-up through 5 years.

Upon completion of the Post Approval Study, patients will continue to be enrolled in the National TVT Registry.

11.0 Benefit-Risk Conclusion

A substantial body of data totaling 1861.9 patient-years of follow-up has been analyzed from over 900 patients treated with the MitraClip Device across the clinical program (2003-2012). In an overall benefit-risk assessment, the magnitude and duration of probable benefit must outweigh the extent of probable harm as measured by procedure and device-related complications. Based on the amassed evidence, the benefits of the MitraClip therapy which include significant and durable MR reduction, left ventricular reverse remodeling, decreased heart failure hospitalizations, improved symptoms and improved quality of life, clearly outweigh the risks of procedural and device-related complications.

Standard of care treatment for clinically significant mitral regurgitation is mitral valve surgery. Patients deemed to be too high risk for mitral valve surgery have limited treatment options. These patients are often offered only medical management for palliative care. Medical management does not prevent further decline in cardiovascular function or increase survival.

The MitraClip Device reduces mitral regurgitation through a percutaneous approach without the need for cardiac arrest. Relatively short procedure times and low device complication rates support its safe use. In the Integrated High Surgical Risk Cohort, greater than 85% of patients experienced acute MR reduction. Reduction in MR was accompanied by meaningful improvements in left ventricular function, NYHA Class symptoms and heart failure hospitalization rates. The magnitudes of clinical benefits were similar in males and females, and in patients with DMR or FMR. Further, these benefits were consistently observed in the MitraClip group in the EVEREST II RCT where although patients differed with respect to baseline risk, the severity of MR and their valve anatomic characteristics were similar to the Integrated High Surgical Risk Cohort. The MitraClip effect on the measures of clinical benefit in both the Integrated High Surgical Risk Cohort and the RCT MitraClip group, though smaller than surgery, were consistent with the expected benefits from the mechanical reduction of MR. Reduction in MR, favorable LV reverse remodeling and improvement in NYHA Class symptoms were sustained through 2 years. These benefits exceed what may be expected from medical management.

Benefits of the MitraClip Device clearly outweigh the risks of use. The 30 day procedural mortality rate was significantly lower than expected based upon the STS score. Survival was no worse than that observed in medically treated patients in the Duke Cardiovascular Database providing evidence that mortality is not increased compared to the medically treated population. Adjudicated major adverse events were consistent with the patient population and did not suggest any unique risk for the device. The complication rate and device related safety events are minimal. Overall safety and post-marketing experience also

support safe use of the device. This favorable safety profile is indispensable to the high surgical risk patient niche for whom the risks of conventional surgery and prolonged recovery greatly outweigh any potential surgical benefits and for whom medical management provides only palliative care.

The appropriate benefit–risk profile in support of this decision will be reinforced by a rigorous post-approval clinical program and robust training regimen based upon a decade of MitraClip clinical experience. The commitment to an extensive post-approval clinical program will be supported by 5-year IDE follow-up, entry of all patients in a TVT National MitraClip Registry, and rapid initiation of a formal post-approval study. In collaboration with FDA, the post-approval study is proposed to consist of a prospective, multicenter trial following approximately 2400 patients with functional and degenerative MR through 5 years.

In the commercial setting, a formal physician education and training program centered on a multidisciplinary heart team and support personnel will ensure ongoing safety of the MitraClip Device. The MitraClip training program has been instituted since the beginning of the MitraClip clinical trial program in 2003, with considerable development over the last ten years. The comprehensive training will be conducted through a series of prescribed modules including a MitraClip therapy orientation, device and procedural training, patient selection, and post-procedural follow-up.

As previously stated, the proposed indications for use as supported by data from the high surgical risk cohort will target patients with symptomatic significant MR (3+ or 4+) who have been determined by a cardiac surgeon to be at too high risk for open mitral valve surgery and in whom existing co-morbidities would not preclude the expected benefit from correction of MR. Thus the product labeling would support approval for use in those individuals who should appropriately be considered high surgical risk and are not candidates for mitral valve surgery.

In sum, the totality of evidence based upon premarket data provides a reasonable assurance of safety and effectiveness in the proposed high surgical risk population to support PMA approval of the MitraClip device. The MitraClip therapy offers a unique safety advantage, addresses the distinct treatment needs of a difficult-to-treat patient population, and attains safety rates that are no worse than the currently accepted modality of treatment in a less risky patient population. Conclusively, the MitraClip technology offers a compelling therapeutic option for the high surgical risk patient population, which would otherwise lack a safe alternative to treat MR.

12.0 References

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Appendices

Appendix A Assessment of Mitral Regurgitation Severity in EVEREST II Trials

For the purpose of assessing severity of mitral regurgitation by echocardiography pre- and post-procedure for the EVEREST II trials, mitral regurgitation severity was determined based on the American Society of Echocardiography (ASE) Recommendations for Evaluation of The Severity of Native Valvular Regurgitation with Two-Dimensional and Doppler Echocardiography²¹. The Echocardiography Core Laboratory makes all of the measurements required to determine the MR severity score using the integrative method based on qualitative and quantitative data as described in the ASE guidelines. Table 66 outlines the guidelines used for determining MR severity grade. When two regurgitant jets are noted on the echocardiographic exam of a mitral valve after treatment (surgery or MitraClip), the jet with the greater regurgitation severity rating is recorded on the Case Report Form. The Mild to Moderate rating is used following the ASE guidelines that states: *“The wording chosen for expressing the degree of MR, which is a continuum best defined by quantitative measurements, can include qualifiers such as mild-to-moderate to describe the lowest end of the moderate range, moderate-to-severe to describe the upper end of the moderate range.”*

Table 66: Mitral Regurgitation Severity Scoring

Variable	Mild 1	Mild to Moderate 1-2	Moderate 2	Moderate to Severe 3	Severe 4
Color Flow Jet	Small (<4 cm ² or <10% of LA area) and central	Central, moderate (4 - 6 cm ² or 10-30% of LA area)	Central, large (>6 < 8 cm ² or >30%<40% of LA area) or Eccentric reaching 1 st PV	Central, large (>8 cm ² or >40% of LA area) or Eccentric reaching 2 nd PV	Central, large (>8 cm ² or >40% of LA area) or Eccentric reaching 2 nd PV
Pulmonary Vein Flow	Systolic dominant	Diastolic dominant	All diastolic	All diastolic	Systolic flow reversal
Regurgitant Volume (mL/beat)	< 30	30 - 44	45 - 59	45 - 59	≥60
Regurgitant Fraction (%)	< 30	30 - 39	40 - 49	40 - 49	≥50
EROA (cm ²)	< 0.20	0.20-0.29	0.30-0.39	0.30-0.39	≥ 0.40
Vena contracta width	< 0.5 cm			≥0.5 cm	

Table 67 provides the portions of the ASE document that describe the integrative method for the assessment of MR severity that are followed in the EVEREST II trials. The ASE Task Force that authored this document stated, “The approach to evaluation of MR severity ideally integrates multiple parameters rather than depends on a single measurement. This helps minimize the effects of technical or measurement errors that are inherent to each method...” The EVEREST II trials follow this strategy.

If the MR severity determination for patient eligibility (screening) used both transthoracic (TTE) and transesophageal (TEE) echocardiograms to qualify the patient for the EVEREST study, then the overall MR grade at Baseline were based on both the TEE and TTE jet characteristics.

Table 67: Integrative Method for the Assessment of MR Severity

(reproduced from: Zoghbi et al.²¹)

Integrative Approach to Assessment of Mitral Regurgitation Severity

“Based on data in the literature and consensus of the committee members, the Task Force proposes a scheme of specific signs ($\geq 90\%$ specificity), along with supportive signs and quantitative parameters to help grade the severity of MR (**Table 3**). In applying this scheme, the Task Force also wishes to recognize the following. The specific signs have inherently a high positive predictive value for the severity of regurgitation. On the other hand, the supportive signs or clues may be helpful in consolidating the impression of the degree of MR, although their predictive value is more modest, since they are influenced by several factors. It is the consensus of the committee members that the process of grading MR should be comprehensive, using a combination of clues, signs and measurements obtained by Doppler-echocardiography. If the MR is definitely determined as a mild or less using these signs, no further measurement is required. If there are signs suggesting that the MR is more than mild and the quality of the data lends itself to quantitation, it is desirable for echocardiographers with experience in quantitative methods to determine quantitatively the degree of MR, including the regurgitant volume and fraction as descriptors of volume overload and the effective regurgitant orifice as a descriptor of the lesion severity. It is also the consensus of the Task Force that the wording chosen for expressing the degree of MR, which is a continuum best defined by quantitative measurements, can include qualifiers such as mild-to-moderate to describe the lowest end of the moderate range, moderate-to-severe to describe the upper end of the moderate range. Finally, it is important to stress that when the evidence from the different parameters is congruent, it is easy to grade MR severity with confidence. When different parameters are contradictory, one must look carefully for technical and physiologic reasons to explain any discrepancies and rely on the components that have the best inherent quality of the primary data and are the most accurate considering the underlying physiologic condition.”

Table 3 Application of specific and supportive signs, and quantitative parameters in the grading of mitral regurgitation severity

	Mild	Moderate	Severe
Specific signs of severity	<ul style="list-style-type: none"> • Small central jet < 4 cm² • Vena contracta width <0.3 cm • No or minimal flow convergence 	Signs of MR > mild present, but no criteria for severe MR	<ul style="list-style-type: none"> • Vena contracta width ≥ 0.7 cm <i>with</i> large central MR jet (area >40% of LA) or with a wall-impinging jet of any size, swirling in LA^ψ • Large flow convergence^ζ • Systolic reversal in pulmonary veins • Prominent flail MV leaflet or ruptured papillary muscle
Supportive signs	<ul style="list-style-type: none"> • Systolic dominant flow in pulmonary veins • A-wave dominant mitral inflow^φ • Soft density, parabolic CW Doppler MR signal • Normal LV size* 	Intermediate signs/findings	<ul style="list-style-type: none"> • Dense, triangular CW Doppler MR jet • E-wave dominant mitral inflow (E > 1.2 m/s)^φ • Enlarged LV and LA size**, (particularly when normal function is present).
Quantitative parameters			
R Vol (ml/beat)	< 30	30-44	≥ 60
RF (%)	< 30	30-39	≥ 50
EROA (cm ²)	< 0.20	0.20-0.29	≥ 0.40
		0.30-0.39	

CW, Continuous wave; EROA, effective regurgitant orifice area; LA, left atrium; LV, left ventricle; MV, mitral valve; MR, mitral regurgitation; R Vol, regurgitant volume; RF, regurgitant fraction.

* LV size applied only to chronic lesions. Normal 2D measurements: LV minor axis ≤ 2.8 cm/m², LV end-diastolic volume ≤ 82 ml/m², maximal LA antero-posterior diameter ≤ 2.8 cm/m², maximal LA volume ≤ 36 ml/m² (2;33;35).

** In the absence of other etiologies of LV and LA dilation and acute MR.

^ψ At a Nyquist limit of 50-60 cm/s.

^φ Usually above 50 years of age or in conditions of impaired relaxation, in the absence of mitral stenosis or other causes of elevated LA pressure.

^ζ Minimal and large flow convergence defined as a convergence radius < 0.4 cm and ≤ 0.9 cm for central jets, respectively, with a baseline shift at a Nyquist of 40 cm/s; Cut-offs for eccentric jets are higher, and should be angle corrected (see text).

^φ Quantitative parameters can help sub-classify the moderate regurgitation group into mild-to-moderate and moderate-to-severe as shown.

Appendix B Valve Anatomic Criteria

The EVEREST II RCT, EVEREST II HRR and REALISM studies enrolled patients with either degenerative or functional MR. Patients were excluded if they met the following valve anatomic criteria.

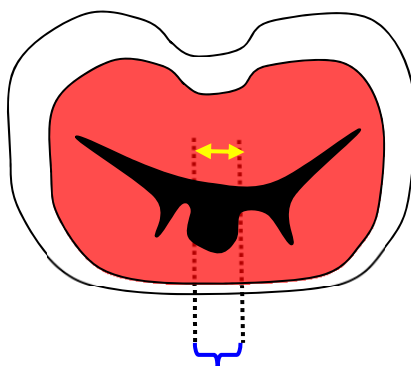
1. If leaflet flail is present (degenerative MR):
 - Flail Width: the width of the flail segment is greater than or equal to 15 mm, as defined below, or
 - Flail Gap: the flail gap is greater than or equal to 10 mm, as defined below.
2. If leaflet tethering is present (functional MR):
 - Coaptation Length: the vertical coaptation length is less than 2 mm, as defined below.
 - Coaptation Depth: the mitral valve coaptation depth is more than 11 mm, as defined below (this was a surgical exclusion criterion and therefore was not an exclusion for EVEREST II HRR and REALISM studies)
3. Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR. This may include:
 - Evidence of calcification in the grasping area of the A2 and/or P2 scallops
 - Presence of a significant cleft of A2 or P2 scallops
 - More than one anatomic criteria dimensionally near the exclusion limits
 - Bileaflet flail or severe bileaflet prolapse
 - Lack of both primary and secondary chordal support
4. Mitral valve orifice area < 4.0 cm²

Leaflet Flail:

Flail is defined as when a leaflet has both ruptured chordae and a free edge that extends above the opposing leaflet or above the plane of the annulus during systole:

Flail width:

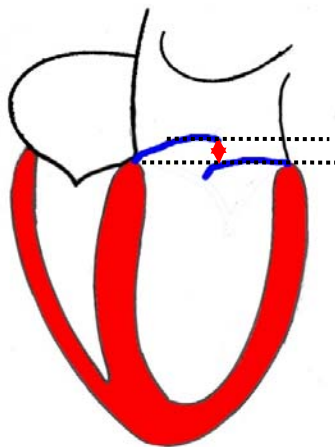
Flail width is defined as the width of flail leaflet segment as measured along the line of coaptation in the short axis view.



Flail Width

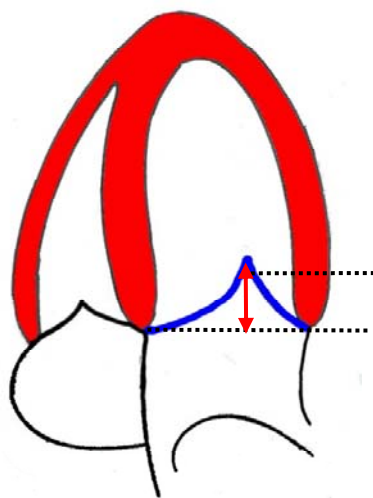
Flail Gap:

Flail gap is defined as the greatest distance between the ventricular side of the flail leaflet segment to the atrial side of the opposing leaflet edge. Flail Gap is illustrated in the figure below. This distance is measured perpendicular to the plane of the annulus in two views and the largest measurement is used. The two TEE views for measurement are the four-chamber long axis (LAX) view and the left ventricular outflow tract (LVOT) view.



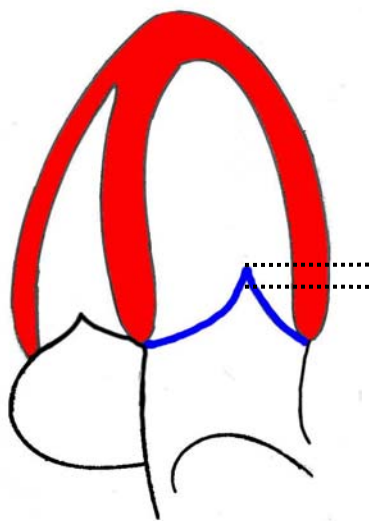
Coaptation Depth

Coaptation depth is defined as the distance from the plane of the mitral valve annulus to the first point of leaflet coaptation during mid systole in the atrial-to-ventricular direction in the four-chamber view.



Coaptation Length:

Coaptation length is defined as the vertical length of leaflets that is in contact, or is available for contact, during mid-systole in the atrial-to-ventricular direction in the four-chamber view.



Appendix C Definition of Adverse Events

Table 68: Procedural Mortality

Event	Definition
Procedural Mortality	All-cause mortality at 30 days or discharge post-MitraClip procedure, whichever is longer

Table 69: Major Adverse Events

Event	Definition
Major Adverse Events	Defined as combined clinical endpoint of death, myocardial infarction (MI), re-operation for failed surgical repair or replacement, non-elective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, ventilation for greater than 48 hours, gastrointestinal (GI) complication requiring surgery, new onset of permanent atrial fibrillation, septicemia, and transfusion of 2 or more units of blood.
Death	All-cause death
Myocardial Infarction	A myocardial infarction (MI) is diagnosed by finding of typical chest pain (> 20 min duration) and any of the following: <ol style="list-style-type: none"> 1. Q wave MI (QMI) (Joint European Society of Cardiology / ACC) <ul style="list-style-type: none"> The development of pathological Q waves on at least two serial ECGs. <ul style="list-style-type: none"> • Pathologic Q waves are defined as any Q waves in leads V1-V3. • Q waves ≥ 3ms in width in leads I, II, aVL, aVF, V4, V5 or V6 (two or more contiguous leads) and must be ≥ 1mm depth. 2. Non-Q wave MI (Joint European Society of Cardiology / ACC) <ol style="list-style-type: none"> a. Non-procedural CK-MB elevation greater than or equal to two times the upper limit of normal in the absence of new pathological Q waves. b. Post-endovascular intervention: CK-MB elevation greater than or equal to three times the upper limit of normal in the absence of new pathological Q waves. c. Post surgery: CK-MB elevation greater than or equal to five times the upper limit of normal in the absence of new pathological Q waves.
Re-operation for failed surgical repair or replacement	Failed surgical repair or replacement is defined as any failure of the surgical mitral valve repair or replacement including suture tear out, stitch rupture, creation of left ventricle outflow tract obstruction, creation of hemolysis, failed chordal shortening or replacement, annuloplasty ring dehiscence, dehiscence, failure of papillary muscle repair or failure of any surgical correction of the mitral valve. Also included are causes not intrinsic to the prosthesis itself such as inappropriate sizing, prosthesis dehiscence, perivalvular leak, and leaflet entrapment by suture and pannus.
Non-elective cardiovascular surgery for adverse events	Cardiovascular surgery for adverse events is defined as cardiovascular surgery performed for adverse events including: tamponade, major vessel perforation or injury, Device detachment from one or both leaflets, Device migration, Device thrombosis or other Device malfunctions which may result in worsening of mitral regurgitation, or injury to the leaflets. Not included is vascular surgical repair at the site of venous access for the CVRS procedure or the site used for peripheral cardiopulmonary bypass in the surgery patients. The priority of surgery is defined as: <ol style="list-style-type: none"> 1. <u>Elective</u>: Surgical procedure not requiring immediate attention and performed when hospital and/or patients schedules allow. 2. <u>Urgent</u>: Must have surgery within 24 hours due to patient condition. 3. <u>Emergency</u>: Immediate need for surgery to preserve life.

Event	Definition
Stroke	A neurological deficit lasting more than 24 hours, or lasting 24 hours or less with a brain imaging study showing infarction.
Renal failure	New need for dialysis or a creatinine increasing to 3.5 mg/dL or greater. Not included as renal failure is any renal dysfunction defined as an increase of creatinine over 1.0 mg/dL over the baseline.
Deep wound infection	Deep wound infection involving muscle, bone and/or mediastinum that requires opening of the wound with excision of tissue.
Ventilation > 48 hours	Pulmonary insufficiency requiring ventilatory support for greater than 48 hours post-operatively or post-catheterization.
GI complication requiring surgery	Post-operative occurrence of any GI complication. Requiring (receiving) surgical intervention including cholecystitis requiring cholecystectomy or mesenteric ischemia requiring surgical exploration.
New onset of permanent AF	Presence of atrial fibrillation that cannot be terminated by cardioversion or can only be terminated for brief intervals, or lasts through the 12-month follow-up without cardioversion being attempted.
Septicemia	Systemic infection requiring hospitalization and treatment with antibiotics.
Transfusion ≥ 2 units of blood	Includes only pRBCs, FFPs, Cryoprecipitate, and Platelets. Does not include use of cell saver, cardioplegia or autologous blood.

Table 70: Other Secondary Safety Endpoints

Event	Definition
Vascular Complications	Includes: <ul style="list-style-type: none"> • Hematoma at access site > 6 cm • Retroperitoneal hematoma • Arterio-venous fistula • Symptomatic peripheral ischemia/nerve injury with clinical signs or symptoms lasting > 24 hours • Vascular surgical repair at catheter access sites • Pulmonary embolism • Ipsilateral deep vein thrombus • Access site-related infection requiring intravenous antibiotics and/or extended hospitalization
Major Bleeding Complications	Procedure related bleeding that requires a transfusion of ≥ 2 units of blood products and/or surgical intervention
Non-cerebral thromboembolism	Any thrombus or thromboembolism in the vasculature (excluding CNS events) or in the investigational device or any commercially available implant used during surgery confirmed by standard clinical and laboratory testing and which requires treatment
Dysrhythmias	Occurrence of dysrhythmias including all new onset of atrial fibrillation (persistent or permanent) and heart block requiring placement of a permanent pacemaker at 12 months
Endocarditis	Diagnosis of endocarditis based on the Duke criteria as either: Definite, Possible or Rejected
Thrombosis	Evidence of the formation of an independently moving thrombus on any part of the Device or any commercially available implant used during surgery by echocardiography or fluoroscopy. If the Device is explanted or an autopsy is performed this diagnosis should be confirmed.
Hemolysis	New onset of anemia associated with laboratory evidence of red cell destruction. Diagnosis is confirmed when the plasma free hemoglobin is greater than 40 mg/dL on two measures within 24 hours, or on one

Event	Definition
	measure if intervention is initiated based on other clinical symptoms. <i>Major:</i> Requires intervention with red blood cell transfusion or other hematocrit increasing measures in the absence of other obvious bleeding. <i>Minor:</i> Does not require intervention
Atrial Septal Defect	Clinically significant ASD as a result of the endovascular procedure requiring repair by intervention
Mitral Valve Stenosis	Defined as echocardiographic evidence of mitral stenosis as determined by mitral valve orifice area less than 1.5 cm ² at 30 days and 12 months by the ECL
Heart failure hospitalization	Reported based on a discharge diagnosis of heart failure

Appendix D High Risk Criteria in the EVEREST II High Risk Registry and REALISM Studies

Patients enrolling in the EVEREST II HRR and REALISM studies had to have a surgical mortality risk prediction of at least 12% based on either one of the following:

- (1) Society of Thoracic Surgeons (STS) mortality risk of at least 12%, or
- (2) Assigned a surgical mortality risk prediction of at least 12% by a cardiac surgeon based on the presence of one or more of pre-specified surgical risk factors listed below:
 - a. Porcelain aorta or mobile ascending aortic atheroma
 - b. Post-radiation mediastinum
 - c. Previous mediastinitis
 - d. Functional MR with EF<40
 - e. Over 75 years old with EF<40
 - f. Re-operation with patent grafts
 - g. Two or more prior chest surgeries
 - h. Hepatic cirrhosis
 - i. Three or more of the following STS high risk factors:
 - i. Creatinine > 2.5 mg/dL
 - ii. Prior chest surgery
 - iii. Age over 75
 - iv. EF<35

The method of assessing risk based on the STS calculator or surgeon assessment is an accepted method, and documented in the VARC-2 Consensus document (Kappetein et al, J Am Coll Cardiol 2012;60:1438-54)

STS Risk Calculator:



I. Introduction

The Society of Thoracic Surgeons' risk models predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables. The models are primarily used to adjust for case mix when comparing outcomes across institutions with different patient populations. Such comparisons are provided in the Database reports received by STS Database participants. The STS models are also used by physicians and patients as tools for understanding the possible risks of surgery. As these risks are solely statistical estimates, they should be supplemented by the professional judgment of the patients' healthcare provider, particularly their cardiac surgeon.

This overview is provided as background to help users of the online STS risk calculator understand and interpret the results. Throughout this document, variable short names are used frequently. Detailed information on the STS variables, including variable short names and clinical definitions can be found at the STS website - <http://www.sts.org> under the STS National Database tab, Data Managers Section. Brief definitions are also available by clicking the "definitions" link on the risk calculator web page.

II. Surgical Procedures

The STS currently has three risk models: CABG, Valve, and Valve+CABG. The models apply to seven specific surgical procedure classifications:

CABG model

- | | |
|------------------------------------|-------------|
| 1. Isolated Coronary Artery Bypass | (CABG Only) |
|------------------------------------|-------------|

Valve model

- | | |
|--------------------------------------|--------------|
| 2. Isolated Aortic Valve Replacement | (AV Replace) |
| 3. Isolated Mitral Valve Replacement | (MV Replace) |
| 4. Isolated Mitral Valve Repair | (MV Repair) |

Valve+CABG model

- | | |
|------------------------------------|---------------------|
| 5. Aortic Valve Replacement + CABG | (AV Replace + CABG) |
| 6. Mitral Valve Replacement + CABG | (MV Replace + CABG) |
| 7. Mitral Valve Repair + CABG | (MV Repair + CABG) |

See Table 3 below for detailed definitions of these procedure classifications.

NOTE: A predicted risk value will NOT be calculated for any procedure that does not fall into one of these precisely defined categories.

III. About the Current Models

The current models were developed during the fall of 2007 using STS Adult Cardiac Surgery Database records for surgical procedures taking place between January 1, 2002 – December 31, 2006. Risk models were developed for the nine endpoints defined in Table 1:

Table 1. Definition of STS Risk Model Outcomes

Endpoint	Description
Operative Mortality	STS v2.61 Sequence number 3050 (MtOpD): Operative mortality includes both (1) all deaths occurring during the hospitalization in which the operation was performed, even if after 30 days; and (2) those deaths occurring after discharge from the hospital, but within 30 days of the procedure unless the cause of death is clearly unrelated to the operation.
Permanent Stroke	STS v2.61 Sequence number 2830 (CNStrokP): Postoperative stroke (i.e., any confirmed neurological deficit of abrupt onset caused by a disturbance in cerebral blood supply) that did not resolve within 24 hours.
Renal Failure	STS v2.61 Sequence number 2890 (CRenFail): Acute or worsening renal failure resulting in one or more of the following: 1. Increase of serum creatinine to > 2.0, and 2x most recent preoperative creatinine level. 2. A new requirement for dialysis postoperatively.
Prolonged Ventilation > 24 hours	STS v2.61 Sequence number 2860 (CPVntLng): Prolonged pulmonary ventilator > 24 hours. Include (but not limited to) causes such as ARDS, pulmonary edema, and/or any patient requiring mechanical ventilation > 24 hours postoperatively.
Deep Sternal Wound Infection	STS v2.61 Sequence number 2780 (CISDeep): Deep sternal infection, within 30 days postoperatively, involving muscle, bone, and/or mediastinum REQUIRING OPERATIVE INTERVENTION. Must have ALL of the following conditions: 1. Wound opened with excision of tissue (I&D) or re-exploration of mediastinum 2. Positive culture 3. Treatment with antibiotics.
Reoperation for any reason	STS v2.61 Sequence numbers 2720 (COpReBld), 2730 (COpReVlv), 2740 (COpReGft), 2750 (COpReOth), 2760 (COpReNon): Reoperation for bleeding/tamponade, valvular dysfunction, graft occlusion, other cardiac reason, or non-cardiac reason
Major Morbidity or Operative Mortality	A composite endpoint defined as any of the outcomes listed in the first six rows of this table.
Short Stay: PLOS < 6 days *	Discharged alive and within 5 days of surgery
Long Stay: PLOS > 14 days	Failure to be discharged within 14 days of surgery

*NOTE: The definition of the short patient length-of-stay endpoint differs from previous versions of the STS risk model. In the new definition, patients must be discharged alive in order to receive credit for a PLOS < 6 days.

See Table 4 below for listings of the STS variables contained in each of the STS models.

IV. Patient Population

The models can be applied to all adult patients who fall into one of the surgical procedure populations described in Table 3 below, except as follows:

- The model will only calculate a predicted risk value for adult patients age 18 to 110 years.
- The models will only calculate a predicted risk value for those patients for which both age and gender are known.
- The models for renal failure will NOT calculate a predicted risk value for any patients who are on dialysis preoperatively.

V. Missing Data Handling

Missing Data

It is important to understand how missing data values are handled when the STS risk-adjustment models are applied to patients with incomplete data. With the exception of age and gender, missing data values are imputed by assigning a likely substitute value. The algorithm used for missing data imputation is described below.

Required variables: Age and gender are required variables for all models. If either is missing, no value for predicted risk will be calculated.

Categorical variables: Missing data are generally assumed to have the lowest risk category. For example, if diabetes was not coded, it would be assumed to be "No"; if procedure priority were not coded, the procedure would be assumed to be "Elective." In most cases, the lowest risk category is also the most frequent.

Continuous variables: Table 2 shows the values assigned to missing data for continuous model variables.

Table 2. Imputation of Missing Continuous Variables

Model Variable	Model Imputation Information
Body Surface Area (BSA)	If gender is "Male" set BSA = 2.00m ² If gender is "Female" set BSA = 1.75m ²
Ejection Fraction (EF)	<u>CABG Model</u> If CHF is no or missing, set EF = 50% If CHF is yes and gender is Male, set EF = 35% If CHF is yes and gender is Female, set EF = 45% <u>Valve Model</u> Set EF = 50% <u>Valve+CABG Model</u> If CHF is yes and gender is Male, set EF = 40% Otherwise, set EF = 50%
Last Preop Creatinine	Set creat1st = 1.0

VI. Predicted Risk Values

After information has been entered on a given case, the online STS risk calculator provides a risk percentage for each of the outcomes. The risk percentage is the estimated percentage estimates the chance of a specific outcome for a patient with the indicated risk factors. Please note that the calculator updates the risk percentage for each outcome *as each question is answered*; therefore, the most reliable risk percentage will appear only after all available data have been entered.

A note on interpretation of values

The inherent limitations of statistical risk-adjustment models should be kept in mind when interpreting risk percentage values for an individual patient. Risk adjustment attempts to take into account as many of the patient's risk factors as possible. However, there are potentially difficult-to-measure factors that are not included in the STS risk-adjustment models and which may increase or decrease a patient's risk of an adverse outcome.

As with any statistical estimates, the risk percentage values should be supplemented by the professional judgment of the patients' healthcare provider, particularly their cardiac surgeon.

Table 3. Procedure Identification for Risk Adjustment – Data Version 2.61

Variable Short Name	CABG Only	AV Replace	AV Replace + CABG	MV Replace	MV Replace + CABG	MV Repair	MV Repair + CABG
OpCAB	Yes	No or Missing	Yes	No or Missing	Yes	No or Missing	Yes
OpValve	No or Missing	Yes	Yes	Yes	Yes	Yes	Yes
VAD	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OpAortic	No or Missing	Replacement	Replacement	No or Missing	No or Missing	No or Missing	No or Missing
OpMitral	No or Missing	No or Missing	No or Missing	Replacement	Replacement	**	**
OpTricus	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OpPulm	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OpONCard	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OpOCard	Do not use OpOCard for exclusions. Use specific variables below.						
OCarLVA	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarVSD	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarASD	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarBati	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarSVR	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarCong	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarLasr	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarTrma	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarCrTx	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarACD	Do not use OCarACD for exclusions.						
OCarAFib	None or Missing	None or Missing	None or Missing	None or Missing	None or Missing	None or Missing	None or Missing
ONCAoAn	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing
OCarOthr	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing	No or Missing

** Annuloplasty only or Reconstruction w/ Annuloplasty or Reconstruction w/out Annuloplasty

Table 4. STS Risk Model Variables – Data Version 2.61 – Variable Name (Sequence Number)

CAB	Operative Mortality	Stroke	Renal Failure	Prolonged Ventilation	Deep Stern Infx	Reop	Mortality/Morbidity	Length of Stay>14	Length of Stay<6
B. Demographics									
Patient Age (140)	x	x	x	x	x	x	x	x	x
Gender (150)	x	x	x	x	x	x	x	x	x
RaceBlack (192)		x	x	x	x	x	x	x	x
RaceAsian (193)		x	x	x	x	x	x	x	x
Ethnicity (199)		x	x	x	x	x	x	x	x
D. Risk Factors									
Weight (350)	x	x	x	x	x	x	x	x	x
Height (360)	x	x	x	x	x	x	x	x	x
Diabetes (400)	x	x	x	x	x	x	x	x	x
Diabetes Control (410)	x	x	x	x	x	x	x	x	x
Last Preop Creatinine Level (430)	x	x	x	x	x	x	x	x	x
Renal Failure-Dialysis (450)	x	x	NA	x	x	x	x	x	x
Hypertension (460)		x	x	x			x	x	x
Infectious Endocarditis Type (500)									
Chronic Lung Disease (510)	x		x	x	x	x	x	x	x
Immunosuppressive Treatment (520)	x		x	x		x	x	x	x
Peripheral Arterial Disease (530)	x	x	x	x	x	x	x	x	x
Cerebrovascular Disease (540)	x	x	x	x		x	x	x	x
Cerebrovascular Accident (552)	x	x	x	x		x	x	x	x
E. Previous Interventions									
Previous CAB (600)	x	x	x	x	x	x	x	x	x
Previous Valve (610)	x	x	x	x	x	x	x	x	x
Previous PCI Interval (670)	x		x	x		x	x	x	x
F. Preoperative Cardiac Status									
Previous Myocardial Infarction Timing (760)	x	x	x	x			x	x	x
Heart Failure (770)	x		x	x	x	x	x	x	x
Classification-NYHA (775)	x		x	x	x	x	x	x	x
Cardiac Presentation on Admission (791)	x		x	x					
Cardiogenic Shock (810)	x	x	x	x		x	x	x	x
Resuscitation (830)	x	x	x	x	x	x	x	x	x
Arrhythmia Afib / Aflutter (853)	x	x	x	x		x	x	x	x
G. Preoperative Medications									
Inotropes (970)	x		x	x		x	x	x	x
H. Hemodynamics and Cath									
Number of Diseased Vessels (1050)	x	x	x	x	x	x	x	x	x
Left Main Disease (1060)				x			x		
Ejection Fraction (1080)	x	x	x	x	x	x	x	x	x
Aortic Stenosis (1120)				x			x	x	x
Mitral Stenosis (1140)									
Aortic Insufficiency (1170)									x
Mitral Insufficiency (1180)	x			x		x	x	x	x
Tricuspid Insufficiency (1190)			x	x			x		x
I. Operative									
Incidence (1230)	x	x	x	x	x	x	x	x	x
Status (1240)	x	x	x	x	x	x	x	x	x
IABP-Timing (1440)	x		x	x		x	x	x	x

Valve (AVRepl, MV Repl, MVRepr)	Operative Mortality	Stroke	Renal Failure	Prolonged Ventilation	Deep Stern Infx	Reop	Mortality/Morbidity	Length of Stay>14	Length of Stay<6
B. Demographics									
Patient Age (140)	x	x	x	x	x	x	x	x	x
Gender (150)	x	x	x	x	x	x	x	x	x
RaceBlack (192)		x	x	x		x	x	x	x
RaceAsian (193)									
Ethnicity (199)		x	x	x		x	x	x	x
D. Risk Factors									
Weight (350)	x	x	x	x	x	x	x	x	x
Height (360)	x	x	x	x	x	x	x	x	x
Diabetes (400)	x		x	x	x	x	x	x	x
Diabetes Control (410)	x		x	x	x	x	x	x	x
Last Preop Creatinine Level (430)	x	x	x	x		x	x	x	x
Renal Failure-Dialysis (450)	x	x	NA	x	x	x	x	x	x
Hypertension (460)	x	x	x	x			x		x
Infectious Endocarditis Type (500)	x	x	x	x		x	x	x	x
Chronic Lung Disease (510)	x		x	x	x	x	x	x	x
Immunosuppressive Treatment (520)	x		x				x	x	
Peripheral Arterial Disease (530)	x	x				x	x	x	x
Cerebrovascular Disease (540)		x	x	x		x	x	x	x
Cerebrovascular Accident (552)		x	x	x		x	x	x	x
E. Previous Interventions									
Previous CAB (600)	x	x	x	x	x	x	x	x	x
Previous Valve (610)	x	x	x	x	x	x	x	x	x
Previous PCI Interval (670)									
F. Preoperative Cardiac Status									
Previous Myocardial Infarction Timing (760)	x			x		x	x	x	x
Heart Failure (770)	x		x	x		x	x	x	x
Classification-NYHA (775)	x		x	x		x	x	x	x
Cardiac Presentation on Admission (791)	x								
Cardiogenic Shock (810)	x	x		x		x	x	x	
Resuscitation (830)	x	x	x	x		x	x	x	x
Arrhythmia Afib / Aflutter (853)	x	x		x		x	x	x	x
G. Preoperative Medications									
Inotropes (970)	x		x	x	x	x	x	x	x
H. Hemodynamics and Cath									
Number of Diseased Vessels (1050)		x		x			x	x	x
Left Main Disease (1060)	x		x		x				
Ejection Fraction (1080)	x		x	x	x	x	x	x	x
Aortic Stenosis (1120)				x		x	x	x	x
Mitral Stenosis (1140)	x								
Aortic Insufficiency (1170)									
Mitral Insufficiency (1180)		x							
Tricuspid Insufficiency (1190)			x	x		x	x	x	x
I. Operative									
Incidence (1230)	x	x	x	x	x	x	x	x	x
Status (1240)	x	x	x	x	x	x	x	x	x
IABP-Timing (1440)	x		x	x	x	x	x	x	x
K. Valve Surgery									
Mitral Procedure (1640)	x	x	x	x	x	x	x	x	x

Valve+CAB (AVRepl+CAB, MVRepl+CAB, MVRepr+CAB)	Operative Mortality	Stroke	Renal Failure	Prolonged Ventilation	Deep Stern Infx	Reop	Mortality/Morbidity	Length of Stay>14	Length of Stay<6
B. Demographics									
Patient Age (140)	x	x	x	x	x	x	x	x	x
Gender (150)	x	x	x	x	x	x	x	x	x
RaceBlack (192)			x	x		x	x	x	x
RaceAsian (193)									
Ethnicity (199)			x	x		x	x	x	x
D. Risk Factors									
Weight (350)	x	x	x	x	x	x	x	x	x
Height (360)	x	x	x	x	x	x	x	x	x
Diabetes (400)	x	x	x	x	x		x	x	x
Diabetes Control (410)	x	x	x	x	x		x	x	x
Last Preop Creatinine Level (430)	x	x	x	x		x	x	x	x
Renal Failure-Dialysis (450)	x	x	NA	x	x	x	x	x	x
Hypertension (460)		x	x	x	x		x	x	x
Infectious Endocarditis Type (500)	x	x	x	x		x	x	x	x
Chronic Lung Disease (510)	x		x	x	x	x	x	x	x
Immunosuppressive Treatment (520)	x		x	x		x	x	x	x
Peripheral Arterial Disease (530)	x	x	x	x		x	x	x	
Cerebrovascular Disease (540)	x	x	x	x	x	x	x	x	x
Cerebrovascular Accident (552)	x	x	x	x	x	x	x	x	x
E. Previous Interventions									
Previous CAB (600)	x	x	x	x	x	x	x	x	x
Previous Valve (610)	x	x	x	x	x	x	x	x	x
Previous PCI Interval (670)									
F. Preoperative Cardiac Status									
Previous Myocardial Infarction Timing (760)	x	x	x	x		x	x	x	
Heart Failure (770)	x	x	x	x		x	x	x	x
Classification-NYHA (775)	x	x	x	x		x	x	x	x
Cardiac Presentation on Admission (791)	x	x	x	x					
Cardiogenic Shock (810)	x	x	x	x		x	x	x	
Resuscitation (830)	x	x	x	x		x	x	x	x
Arrhythmia Afib / Aflutter (853)	x	x	x	x		x	x	x	x
G. Preoperative Medications									
Inotropes (970)	x		x	x		x	x	x	x
H. Hemodynamics and Cath									
Number of Diseased Vessels (1050)	x	x	x	x	x	x	x	x	x
Left Main Disease (1060)	x			x					
Ejection Fraction (1080)	x		x	x		x	x	x	x
Aortic Stenosis (1120)									
Mitral Stenosis (1140)	x							x	
Aortic Insufficiency (1170)									
Mitral Insufficiency (1180)							x		
Tricuspid Insufficiency (1190)	x		x	x			x		x
I. Operative									
Incidence (1230)	x	x	x	x	x	x	x	x	x
Status (1240)	x	x	x	x	x	x	x	x	x
IABP-Timing (1440)	x		x	x		x	x	x	x
K. Valve Surgery									
Mitral Procedure (1640)	x	x	x	x	x	x	x	x	x

STS Adult Cardiac Surgery Database Risk Model Variables – Data Version 2.61

Note, the STS Risk Calculator was changed from version 2.52 to 2.61 in January, 2008.

Logistic EuroSCORE:

For a given patient, the “logistic EuroSCORE” which is the predicted mortality according to the logistic regression equation, can be achieved with the following formula:

$$\text{Predicted mortality} = e^{(\beta_0 + \sum \beta_i X_i)} / 1 + e^{(\beta_0 + \sum \beta_i X_i)}$$

β_0 is the constant of the logistic regression equation = -4.789594

β_i is the coefficient of the variable X_i in the logistic regression equation provided in the table below.

$X_i = 1$ if a categorical risk factor is present and 0 if it is absent

For age, $X_i = 1$ if patient age < 60; X_i increase by one point per year thereafter;

hence for age 59 or less $X_i = 1$, age 60 $X_i = 2$, age 61 $X_i = 3$, *and so on*.

Patient-related factors		Beta
Age	Continuous	0.0666354
Sex	female	0.3304052
Chronic pulmonary disease	longterm use of bronchodilators or steroids for lung disease	0.4931341
Extracardiac arteriopathy	any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	0.6558917
Neurological dysfunction disease	severely affecting ambulation or day-to-day functioning	0.841626
Previous cardiac surgery	requiring opening of the pericardium	1.002625
Serum creatinine	>200m micromol/L preoperatively	0.6521653
Active endocarditis	patient still under antibiotic treatment for endocarditis at the time of surgery	1.101265
Critical preoperative state	any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria <10 ml/hour)	0.9058132
Cardiac-related factors		Beta
Unstable angina	rest angina requiring iv nitrates until arrival in the anaesthetic room	0.5677075
LV dysfunction	moderate or LVEF 30-50%	0.4191643
	poor or LVEF <30	1.094443
Recent myocardial infarct	(<90 days)	0.5460218
Pulmonary hypertension	Systolic PA pressure >60 mmHg	0.7676924
Operation-related factors		Beta
Emergency	carried out on referral before the beginning of the next working day	0.7127953
Other than isolated CABG	major cardiac procedure other than or in addition to CABG	0.5420364
Surgery on thoracic aorta	for disorder of ascending, arch or descending aorta	1.159787
Postinfarct septal rupture		1.462009

Appendix E EVEREST II High Risk Registry (HRR)

E1. EVEREST II HRR - ELIGIBILITY CRITERIA

Inclusion and exclusion criteria for the EVEREST II HRR are listed below:

Inclusion Criteria:

1. Predicted procedural mortality risk calculated using the STS surgical risk calculator of $\geq 12\%$, or if in the judgment of the surgeon Investigator, the patient is considered a high risk surgical candidate due to the presence of one of the following co-morbidities:
 - a. Porcelain aorta or mobile ascending aortic atheroma
 - b. Post-radiation mediastinum
 - c. Previous mediastinitis
 - d. Functional MR with EF $< 40\%$
 - e. Over 75 years old with EF $< 40\%$
 - f. Prior re-operation with patent grafts
 - g. Two or more prior chest surgeries
 - h. Hepatic cirrhosis
 - i. Three or more of the following STS high risk factors:
 - i. Creatinine > 2.5 mg/dL
 - ii. Prior chest surgery
 - iii. Age over 75
 - iv. EF $< 35\%$
2. Age 18 years or older.
3. Symptomatic moderate-to-severe (3+) or severe (4+) chronic mitral valve regurgitation, and in the judgment of the investigator, intervention to reduce MR is likely to provide symptomatic relief for the patient.
4. American Society of Anesthesiologists physical status classification of ASA IV or lower.
5. The primary regurgitant jet originates from malcoaptation of the A2 and P2 scallops of the mitral valve.
6. Male or Female. Female subjects of childbearing potential must have a negative pregnancy test within seven (7) days before the procedure.
7. The subject or the subject's legal representative has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board of the respective clinical site.

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8. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.
 9. Transseptal catheterization is determined to be feasible by the treating physician.

Exclusion Criteria

1. Evidence of an acute myocardial infarction in the prior 2 weeks of the intended treatment (defined as: Q wave or non-Q wave infarction having CK enzymes $\geq 2X$ the upper laboratory normal limit with the presence of a CK-MB elevated above the institution's upper limit of normal).
 2. In the judgment of the Investigator, the femoral vein cannot accommodate a 24 F catheter or presence of ipsilateral DVT.
 3. Ejection fraction $\leq 20\%$, and/or end-systolic dimension > 60 mm.
 4. Mitral valve orifice area $< 4.0\text{cm}^2$.
 5. Mitral valve anatomical exclusions:
 - If leaflet flail is present (degenerative MR):
 - Flail Width: flail segment width greater than or equal to 15 mm
 - Flail Gap: the flail gap is greater than or equal to 10 mm
 - If leaflet tethering is present (functional MR):
 - Coaptation Length: the vertical coaptation length is less than 2 mm
 - Leaflet anatomy which may preclude device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR. This may include:
 - Evidence of calcification in the grasping area of the A2 and/or P2 scallops
 - Presence of a significant cleft of A2 or P2 scallops
 - More than one anatomic criteria dimensionally near the exclusion limits
 - Bileaflet flail or severe bileaflet prolapse
 - Lack of both primary and secondary chordal support
 6. Hemodynamic instability defined as systolic pressure $< 90\text{mmHg}$ without afterload reduction or cardiogenic shock or the need for inotropic support or intra-aortic balloon pump.
 7. Need for emergent or urgent surgery for any reason.
 8. Prior mitral valve leaflet surgery or any currently implanted mechanical prosthetic mitral valve.
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9. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation.
10. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e. noncompliant, perforated).
11. History of bleeding diathesis or coagulopathy or subject will refuse blood transfusions.
12. Active infections requiring current antibiotic therapy; may enroll 2 weeks post discontinuation of antibiotic therapy. Patients must be free from infection prior to treatment. Any required dental work should be completed a minimum of 3 weeks prior to treatment.
13. Intravenous drug abuse or suspected inability to adhere to follow-up.
14. Patients in whom transesophageal echocardiography (TEE) is contraindicated.
15. A known hypersensitivity or contraindication to study or procedure medications which cannot be adequately managed medically.
16. In the judgment of the Investigator, patients for whom the presence of a permanent pacemaker or pacing leads would interfere with placement of the test device or the placement of the test device would disrupt the leads.
17. Currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.

E2. EVEREST II HRR - STUDY COMPLIANCE

Visit compliance in the EVEREST II HRR was high (>98%) through 3 years (Table 71). Clinical follow-up occurred in 94.9% of patients at 1 year and almost 90% of patients at 2 years and 3 years.

Table 71: EVEREST II HRR – Study Compliance

Follow-up Visit	# Visits	# Missed Visit	# Deaths before visit	# Withdrawn before visit	Visit Compliance	Clinical Follow-up Occurred In
30-Day	72	0	6	0	100%	100%
1 Year	56	1	18	3	98.7%	94.9%
2 Years	44	1	26	7	98.6%	89.7%
3 Years	39	1	31	7	98.6%	89.7%

E3. EVEREST II HRR - HIGH SURGICAL RISK CHARACTERISTICS

Patients were considered high surgical risk if their STS calculated risk score was $\geq 12\%$, or if their surgeon investigator deemed that the patient was high risk based on one or more pre-specified surgical risk factors as defined in the study protocol. In the latter case, the surgeon assigned a surgical mortality risk $\geq 12\%$ based on the pre-specified co-morbidities. Of the 78 patients enrolled in the HRR, 48 (61.5%) were enrolled with an STS mortality risk score $\geq 12\%$, and the remaining 30 (38.5%) were deemed high risk ($\geq 12\%$ predicted surgical mortality risk) due to the presence of one or more pre-specified surgical risk factors. Table 72 displays the pre-specified risk factors that qualified patients as high surgical risk in the EVEREST II HRR (N = 30).

Table 72: EVEREST II HRR - Pre-specified Surgical Risk Factor

Pre-Specified Surgical Risk Factor ^a	% Patients (n/N)
Porcelain aorta or mobile ascending aortic atheroma	6.7% (2/30)
Post-radiation mediastinum	3.3% (1/30)
Previous mediastinitis	0.0% (0/30)
Hepatic cirrhosis	6.7% (2/30)
Two or more prior chest surgeries	23.3% (7/30)
Functional MR with LVEF < 40%	33.3% (10/30)
Over 75 years old with LVEF < 40%	20.0% (6/30)
Re-operation with patent grafts	53.5% (16/30)
Three or more STS high risk factors ^b	10.0% (3/30)

^a Patients may be included in more than one category

^b Creatinine > 2.5 mg/dL, prior chest surgery, age over 75, EF < 35%

E4. EVEREST II HRR – SECONDARY SAFETY ENDPOINT RESULTS

The major adverse event rate at 30 days was 26.9%, with transfusions ≥ 2 units comprising the majority of events (17.9%). Stroke, myocardial infarction and prolonged ventilation (> 48 hours) each occurred at a rate of 2.6% and renal failure occurred at a rate of 3.8% at 30 days. There was no incidence of non-elective (urgent/emergent) cardiovascular surgery for adverse events or new onset of persistent atrial fibrillation in this cohort through 1 year. Beyond 30 days through 1 year, patients experienced myocardial infarction and renal failure at rate consistent with this severely co-morbid population.

Major vascular complications occurred at a low rate (2.6%) at 30 days. No additional complications occurred through 1 year.

Thirteen (13) patients or 16.7% experienced a major bleeding complication at 30 days defined as bleeding resulting in transfusion ≥ 2 units or surgery. In 9 patients, the bleeding occurred at the access site, 2 patients experienced GI bleeds and in 2 patients, the bleed location was not specified.

New onset of persistent atrial fibrillation occurred in 5 patients (6.4%) at 30 days, 1 patient (1.3%) experienced AV block requiring a permanent pacemaker, and 2 patients (2.6%) underwent a percutaneous procedure for atrial septal defect. There was no occurrence of non-cerebral thromboembolism, endocarditis, thrombosis or hemolysis at 30 days. The rate of safety events between 30 days and 1 year is consistent with that are commonly observed in this elderly, highly co-morbid population.

Table 73: EVEREST II HRR - CEC Adjudicated Major Adverse Events

Description of Event	% Patients (n/N)	
	30-Day	1-Year
Death ^a	7.7% (6/78)	23.1% (18/78)
Myocardial infarction	2.6% (2/78)	5.1% (4/78)
Re-operation for failed surgical repair or replacement	0.0% (0/78)	0.0% (0/78)
Non-elective cardiovascular surgery for AE	0.0% (0/78)	0.0% (0/78)
Stroke	2.6% (2/78)	2.6% (2/78)
Renal failure	3.8% (3/78)	6.4% (5/78)
Deep wound infection	0.0% (0/78)	0.0% (0/78)
Ventilation > 48 hours	2.6% (2/78)	2.6% (2/78)
GI complication requiring surgery	1.3% (1/78)	3.8% (3/78)
New onset of permanent AF	0.0% (0/78)	0.0% (0/78)
Septicemia	0.0% (0/78)	3.8% (3/78)
Transfusion of ≥ 2 units of blood	17.9% (14/78)	24.4% (19/78)
Total^b	26.9% (21/78)	42.3% (33/78)
Total^b (Excluding Transfusions ≥ 2 units)	12.8% (10/78)	33.3% (26/78)

^a One additional patient died between 30 days and 12 months and is reported in the analysis of the major effectiveness endpoint (this death was reported by the site from an obituary in the local paper); however, this death is not included in this table since it occurred after the patient withdrew from the study

^b Total number of patients may not equal the sum of patients in each row since one patient may experience multiple events

Table 74: EVEREST II HRR - CEC Adjudicated Other Secondary Safety Endpoints

Description of Event	% Patients (n/N)	
	30-Day	1-Year
Major Vascular Complication	2.6% (2/78)	3.8% (3/78)
Major Bleeding Complication	16.7% (13/78)	19.2% (15/78)
Non-Cerebral Thromboembolism	0.0% (0/78)	1.3% (1/78)
New Onset Persistent Atrial Fibrillation	6.4% (5/78)	9.0% (7/78)
Heart Block/Other arrhythmia requiring permanent pacemaker	1.3% (1/78)	1.3% (1/78)
Endocarditis	0.0% (0/78)	1.3% (1/78)
Thrombosis	0.0% (0/78)	0.0% (0/78)
Hemolysis	0.0% (0/78)	0.0% (0/78)
Clinically Significant Atrial Septal Defect (Treated)	2.6% (2/78)	2.6% (2/78)

E5. EVEREST II HRR – ADDITIONAL EFFECTIVENESS RESULTS

Significant improvement in NYHA Class was observed at 1 year in the EVEREST II HRR. Among patients with paired data at baseline and 1 year, the proportion of patients with NYHA Class III or IV reduced from 88.9% at baseline to 25.9% at 1 year. Improvement in both physical and mental components of the SF-36 quality of life by 4.0 and 3.2 points respectively were observed at 1 year.

Table 75: EVEREST II HRR - NYHA Class and Quality of Life at Baseline and 1-Year Patients with Paired Data

Endpoint	Baseline	1-Year
NYHA Functional Class III/IV, % (n/N)	88.9% (48/54)	25.9% (14/54)
Quality of Life, Physical Component Summary (PCS) Score Mean \pm SD (N)	32.1 \pm 9.6 (47)	36.1 \pm 10.8 (47)
Quality of Life, Mental Component Summary (MCS) Score Mean \pm SD (N)	45.5 \pm 12.6 (47)	48.7 \pm 11.9 (47)

A significant decrease in the rate of heart failure hospitalizations (0.65 to 0.36 per patient-year) was observed in the year following the MitraClip procedure compared to the year prior (Table 76).

Table 76: EVEREST II HRR – Heart Failure Hospitalizations

	1-Year Pre-enrollment	Post-discharge through 1-Year	p-value
# Patients	33	12	
# Events	51	22	
Rate per patient-year of follow-up ^a (95% Two-sided Conf Int)	0.65 (0.50, 0.86)	0.36 (0.24, 0.54)	0.0187

^a p-value and confidence interval are obtained from a Poisson regression model

MR severity at baseline and follow up in patients with paired data at baseline and follow-up are summarized in Table 77. At discharge, MR is reduced in a majority of patients (74.7%) to $\leq 2+$ and in 40% of patients to $\leq 1+$. Among patients with paired data at baseline and 1 year, MR reduction was sustained to $\leq 2+$ in 77.8% of patients and to $\leq 1+$ in 31.5% of patients.

**Table 77: EVEREST II HRR - MR Grade at Baseline and Follow-up
Patients with Paired Data at Baseline and Follow-up**

MR Severity	Baseline % (n/N)	Discharge % (n/N)	Baseline % (n/N)	1-Year % (n/N)
0 : None	0.0% (0/75)	0.0% (0/75)	0.0% (0/54)	0.0% (0/54)
1+: Mild	0.0% (0/75)	40.0% (30/75)	0.0% (0/54)	31.5% (17/54)
2+: Moderate	1.3% (1/75)	34.7% (26/75)	1.9% (1/54)	46.3% (25/54)
3+: Moderate-to-severe	77.3% (58/75)	17.3% (13/75)	70.4% (38/54)	16.7% (9/54)
4+: Severe	21.3% (16/75)	8.0% (6/75)	27.8% (15/54)	5.6% (3/54)

Freedom from the combined endpoint of death and MR>2+ at 1 year was 56.4% for the EVEREST II HRR. Freedom from the combined endpoint of death and MR>1+ at 1 year was 23.1% for the EVEREST II HRR.

Appendix F REALISM High Risk

F1. REALISM HIGH RISK - ELIGIBILITY CRITERIA

Inclusion and exclusion criteria for the REALISM High Risk arm are listed below:

Inclusion Criteria:

1. Predicted procedural mortality risk calculated using the STS surgical risk calculator of $\geq 12\%$, or if in the judgment of the surgeon Investigator, the patient is considered a high risk surgical candidate due to the presence of one of the following co-morbidities:
 - a. Porcelain aorta or mobile ascending aortic atheroma
 - b. Post-radiation mediastinum
 - c. Previous mediastinitis
 - d. Functional MR with EF $< 40\%$
 - e. Over 75 years old with EF $< 40\%$
 - f. Prior re-operation with patent grafts
 - g. Two or more prior chest surgeries
 - h. Hepatic cirrhosis
 - i. Three or more of the following STS high risk factors:
 - i. Creatinine > 2.5 mg/dL
 - ii. Prior chest surgery
 - iii. Age over 75
 - iv. EF $< 35\%$
2. Age 18 years or older
3. Symptomatic moderate-to-severe (3+) or severe (4+) chronic mitral valve regurgitation, and in the judgment of the investigator, intervention to reduce MR is likely to provide symptomatic relief for the patient.
4. American Society of Anesthesiologists physical status classification of ASA IV or lower.
5. The primary regurgitant jet originates from malcoaptation of the A2 and P2 scallops of the mitral valve.
6. Male or non-pregnant female.
7. The subject or the subject's legal representative has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board of the respective clinical site.

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8. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.
 9. Transseptal catheterization is determined to be feasible by the treating physician.

Exclusion Criteria

1. Evidence of an acute myocardial infarction in the prior 2 weeks of the intended treatment (defined as: Q wave or non-Q wave infarction having CK enzymes $\geq 2X$ the upper laboratory normal limit with the presence of a CK-MB elevated above the institution's upper limit of normal).
 2. In the judgment of the Investigator, the femoral vein cannot accommodate a 24 F catheter or presence of ipsilateral DVT.
 3. Ejection fraction $< 20\%$, and/or end-systolic dimension > 60 mm.
 4. Mitral valve orifice area $< 4.0\text{cm}^2$.
 5. Mitral valve anatomical exclusions:
 - If leaflet flail is present (degenerative MR):
 - Flail Width: flail segment width greater than or equal to 15 mm
 - Flail Gap: the flail gap is greater than or equal to 10 mm
 - If leaflet tethering is present (functional MR):
 - Coaptation Length: the vertical coaptation length is less than 2 mm
 - Leaflet anatomy which may preclude device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR. This may include:
 - Evidence of calcification in the grasping area of the A2 and/or P2 scallops
 - Presence of a significant cleft of A2 or P2 scallops
 - More than one anatomic criteria dimensionally near the exclusion limits
 - Bileaflet flail or severe bileaflet prolapse
 - Lack of both primary and secondary chordal support
 6. Hemodynamic instability defined as systolic pressure < 90 mmHg without after load reduction or cardiogenic shock or the need for inotropic support or intra-aortic balloon pump.
 7. Need for emergent or urgent surgery for any reason.
 8. Prior mitral valve leaflet surgery or any currently implanted mechanical prosthetic mitral valve.
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9. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
10. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e. noncompliant, perforated).
11. History of bleeding diathesis or coagulopathy or subject will refuse blood transfusions.
12. Active infections requiring current antibiotic therapy (if temporary illness, patients may enroll 2 weeks after discontinuation of antibiotics). Patients must be free from infection prior to treatment. Any required dental work should be completed a minimum of 3 weeks prior to treatment.
13. Intravenous drug abuse or suspected inability to adhere to follow-up.
14. Patients in whom transesophageal echocardiography (TEE) is contraindicated.
15. A known hypersensitivity or contraindication to study or procedure medications which cannot be adequately managed medically.
16. In the judgment of the Investigator, patients in whom the presence of a permanent pacemaker or pacing leads would interfere with placement of the test device or the placement of the test device would disrupt the leads.
17. Currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials].
18. Any concurrent medical condition(s) that in the opinion of the investigator is likely to result in death within 12 months.

F2. REALISM HIGH RISK ARM - STUDY COMPLIANCE

Visit compliance in the REALISM HR arm (N = 273) was high (>97%) through 2 years (Table 78). Clinical follow-up occurred in 92.7% of patients at 1 year. Among patients eligible for a 2-year follow-up visit, clinical follow-up occurred in 94%.

Table 78: REALISM High Risk Arm – Study Compliance

Follow-up Visit	# Visits	# Missed Visit	# Deaths before visit	# Withdrawn before visit	Not Due for Visit	Visit Compliance	Clinical Follow-up Occurred In
30-Day	252	4	12	5	0	98.5%	96.7%
1-Year	191	7	62	13	0	97.3%	92.7%
2 Years	78	1	47	7	140	99.2%	94.0%

F3. REALISM HIGH RISK ARM – BASELINE DEMOGRAPHIC CHARACTERISTICS AND MEDICAL HISTORY

Table 79 shows the baseline demographic characteristics and medical history for patients in the REALISM HR arm. Patients enrolled in the REALISM HR arm were elderly and co-morbid at baseline. The average predicted surgical mortality was 18.2%. The study enrolled patients of both degenerative and functional MR etiologies (27% DMR, 73% FMR).

Table 79: REALISM HR Arm - Baseline Demographic Characteristics and Medical History

Characteristic % (n/N)	REALISM (N = 273)
Age (years), Mean \pm SD (N)	75.5 \pm 10.7 (273)
Patients over 75 years of age	57.1% (156/273)
Female Gender	39.6% (108/273)
Coronary Artery Disease	81.7% (223/273)
Prior Myocardial Infarction	49.3% (134/272)
Atrial Fibrillation History	70.5% (172/244)
Prior Stroke	13.6% (37/273)
Diabetes	39.0% (106/272)
Moderate to Severe Renal Disease	32.6% (89/273)
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O ₂)	27.2% (72/272)
Previous Cardiovascular Surgery	60.1% (164/273)
Previous Percutaneous Coronary Intervention	53.1% (145/273)
NYHA Class III/IV Heart Failure	83.5% (228/273)
Functional MR Etiology	73.3% (200/273)
LV Ejection Fraction (%), Mean \pm SD (N)	45.2 \pm 13.6 (240)
LV Internal Diameter systole (cm), Mean \pm SD (N)	4.5 \pm 1.1 (245)
Predicted Surgical Mortality Risk (%), Mean \pm SD (N)	18.2 \pm 8.5 (273)

F4. REALISM HIGH RISK ARM - HIGH SURGICAL RISK CHARACTERISTICS

Patients were considered high surgical risk if their STS calculated risk score was $\geq 12\%$, or if their surgeon investigator deemed that the patient was high surgical risk based on one or more pre-specified surgical risk factors as defined in the study protocol. In the latter case, the surgeon assigned a surgical mortality risk $\geq 12\%$ based on the pre-specified co-morbidities. Of the 273 patients in the REALISM HR arm, 103 (37.7%) were enrolled with an STS calculated risk score $\geq 12\%$, and the remaining 170 (62.3%) were deemed high surgical risk ($\geq 12\%$ surgical mortality risk) due to the presence of one or more pre-specified surgical risk factors. Table 80 displays the pre-specified risk factors that qualified patients as high surgical risk in the REALISM HR arm (N = 170).

Table 80: REALISM HR Arm - Pre-specified Surgical Risk Factor

Pre-Specified Surgical Risk Factor ^a	% Patients (n/N)
Porcelain aorta or mobile ascending aortic atheroma	2.9% (5/170)
Post-radiation mediastinum	4.1% (7/170)
Previous mediastinitis	0.6% (1/170)
Hepatic cirrhosis	2.4% (4/170)
Two or more prior chest surgeries	20.0% (34/170)
Functional MR with LVEF < 40%	55.3% (94/170)
Over 75 years old with LVEF < 40%	26.5% (45/170)
Re-operation with patent grafts	48.2% (82/170)
Three or more STS high risk factors ^b	7.6% (13/170)

^a Patients may be included in more than one category

^b Creatinine > 2.5 mg/dL, prior chest surgery, age over 75, EF < 35%

F5. REALISM HIGH RISK ARM – SAFETY RESULTS

Primary Safety Endpoint: Procedural Mortality

Eleven (4%) of patients in the REALISM HR arm died within 30 days or discharge, whichever was longer (Table 81). The 97.5% upper confidence bound on the mortality rate (7.1%) is lower than the average predicted surgical mortality risk (18.2%).

Table 81: REALISM HR Arm – Primary Safety Endpoint

	REALISM HR Arm (N = 273)
Observed Procedural Mortality	4.0% (11/273)
97.5% Upper Confidence Bound (UCB) ^a	7.1%
Average Predicted Surgical Mortality (STS or Surgeon Assessed)	18.2% (p < 0.0001)
Average Predicted Surgical Mortality (STS Mortality Risk)	10.5% (p < 0.0001)

^a UCB is based on the Clopper-Pearson method
p-values obtained by Monte-Carlo simulations

Intra-Procedural Results

No intra-procedural deaths were observed. There were no immediate conversions to surgery. No MitraClip Devices embolized during the procedure.

Post-Procedural Results

The mean ICU stay was 1.4 days and the mean hospital stay was 3.0 days with a median of 2 days (Table 82). Approximately 87% of patients were discharged home without the need for professional home healthcare. An additional 6% were discharged home with home healthcare, resulting in a total of 93.4% being discharged home after the MitraClip procedure.

Table 82: REALISM HR Arm– Post-Procedural Results

Post-Procedural Characteristic	REALISM HR Arm (N = 273)
Post-Procedure ICU/CCU/PACU Duration (days)	
Mean \pm SD	1.4 \pm 2.2 (273)
Median	1.0
Post-Procedure Hospital Stay (days)	
Mean \pm SD	3.0 \pm 4.4 (273)
Median	2.0
Discharge Status	
Home without home healthcare	87.5% (239/273)
Home healthcare required	5.9% (16/273)
Skilled nursing/Long-term acute care	2.9% (8/273)
Death	2.2% (6/273)

CEC adjudicated major adverse events are summarized in Table 83. The major adverse event rate at 30 days is 16.5%, with transfusions ≥ 2 units comprising the majority of events (12.1%). The 30-day stroke rate was 2.6% and 30-day rate for prolonged ventilation (> 48 hours) was 2.9%. Renal failure occurred at a rate of 1.1% at 30 days. Myocardial infarction occurred at a rate of 0.7% at 30 days. There was one incidence of non-elective (urgent/emergent) cardiovascular surgery for adverse events - this patient had an unsuccessful MitraClip procedure due to insufficient reduction of MR and damage to the anterior leaflet. There was only one incidence of new onset of permanent atrial fibrillation at 30 days and no incidence of GI complication requiring surgery. Three patients (1.1%) experienced septicemia at 30 days. Beyond 30 days through 1 year, patients experienced safety events at a rate consistent with that which would be expected in this highly co-morbid population.

Major vascular complications occurred at a low rate (3.7%) at 30 days (Table 84). One additional major vascular complication of retroperitoneal hematoma occurred at 71 days. Twenty-one (21) patients or 7.7% experienced a major bleeding complication defined as bleeding resulting in transfusion ≥ 2 units or surgery.

New onset of persistent atrial fibrillation occurred in 4 patients (1.5%) at 30 days, 3 patients (1.1%) experienced AV block requiring a permanent pacemaker, and 4 patients (1.5%) underwent closure of the atrial septal defect (Table 84). There was one occurrence of non-cerebral thromboembolism at 30 days and no occurrence of endocarditis, thrombosis or hemolysis at 30 days. The rate of events between 30 days and 1 year is consistent with that which would be expected in this elderly, highly co-morbid population.

Table 83: REALISM HR Arm - CEC Adjudicated Major Adverse Events

Description of Event	% Patients (n/N)	
	30-Day	1-Year
Death	4.0% (11/273)	22.7% (62/273)
Myocardial infarction	0.7% (2/273)	1.5% (4/273)
Re-operation for failed surgical repair or replacement	0.0% (0/273)	0.0% (0/273)
Non-elective cardiovascular surgery for AE	0.4% (1/273)	0.4% (1/273)
Stroke	2.6% (7/273)	3.7% (10/273)
Renal failure	1.1% (3/273)	5.1% (14/273)
Deep wound infection	0.0% (0/273)	0.0% (0/273)
Ventilation > 48 hours	2.9% (8/273)	6.2% (17/273)
GI complication requiring surgery	0.0% (0/273)	0.7% (2/273)
New onset of permanent AF	0.4% (1/273)	0.4% (1/273)
Septicemia	1.1% (3/273)	4.4% (12/273)
Transfusion of ≥ 2 units of blood	12.1% (33/273)	22.0% (60/273)
Total^a	16.5% (45/273)	36.3% (99/273)
Total^a (Excluding Transfusions ≥ 2 units)	8.1% (22/273)	27.1% (74/273)

^a Total number of patients may not equal the sum of patients in each row since one patient may experience multiple events

Table 84: REALISM HR Arm - Other Secondary Safety Endpoints

Description of Event	% Patients (n/N)	
	30-Day	1-Year
Major Vascular Complication	3.7% (10/273)	4.0% (11/273)
Major Bleeding Complication	7.7% (21/273)	9.5% (26/273)
Non-Cerebral Thromboembolism	0.4% (1/273)	0.4% (1/273)
New Onset Persistent Atrial Fibrillation	1.5% (4/273)	6.2% (17/273)
Heart Block/Other arrhythmia requiring permanent pacemaker	1.1% (3/273)	2.9% (8/273)
Endocarditis	0.0% (0/273)	0.0% (0/273)
Thrombosis	0.0% (0/273)	0.0% (0/273)
Hemolysis	0.0% (0/273)	0.0% (0/273)
Clinically Significant Atrial Septal Defect (Treated)	1.5% (4/273)	3.3% (9/273)

F6. REALISM HIGH RISK ARM – EFFECTIVENESS RESULTS

Implant Success

The MitraClip device was implanted successfully in a majority (95.6%) of REALISM HR patients, with 56.8% implanted with 1 device and 38.8% implanted with 2 devices (see Section 9.2, Table 60).

Left Ventricular Measurements

Left ventricular measurements at baseline and 1 year in patients with ECL assessed measurements at both timepoints are summarized in Table 85. The table demonstrates statistically significant reduction in all four parameters of left ventricular size.

Table 85: REALISM HR Arm – Left Ventricular Size at Baseline and 1 Year Patients with Paired Data

LV Measurement	N	Baseline	1-Year	Difference (1-Year - Baseline)	p-value
LVEDV, ml					
Mean ± SD	149	156.4± 57.4	143.7± 56.6	-12.7± 31.6	< 0.0001
LVIDd, cm					
Mean ± SD	167	5.6± 0.8	5.4± 0.9	-0.2± 0.4	< 0.0001
LVESV, ml					
Mean ± SD	148	88.7± 48.4	81.4± 46.3	-7.3± 23.8	0.0001
LVIDs cm					
Mean ± SD	156	4.4± 1.1	4.3± 1.1	-0.1± 0.5	0.0058

NYHA Class

Significant improvement in NYHA Class was observed at 1 year in the REALISM HR Arm. Among patients with paired data at baseline and 1 year, the proportion of patients with NYHA Class III or IV reduced from 80% at baseline to 14.4% at 1 year. Improvement in both physical and mental component summary scores of the SF-36 quality of life questionnaire were observed at 1 year, by 5.1 and 5.5 points respectively.

Table 86: REALISM HR Arm - NYHA Class and Quality of Life at Baseline and 1-Yr Patients with Paired Data

Endpoint	Baseline	1-Year
NYHA Functional Class III/IV, % (n/N)	80.0% (144/180)	14.4% (26/180)
Quality of Life, Physical Component Summary (PCS) Score Mean ± SD (N)	34.6 ±8.9 (144)	39.7 ±11.3 (144)
Quality of Life, Mental Component Summary (MCS) Score Mean ± SD (N)	44.7 ±13.8 (144)	50.2 ±12.3 (144)

A significant decrease in the rate of heart failure hospitalizations (0.83 to 0.43 per patient-year) was observed in the year following the MitraClip procedure compared to the year prior (Table 87).

Table 87: REALISM HR Arm – Hospitalizations for Heart Failure

	1-Year Pre-enrollment	Post-discharge through 1-Year	p-value
# Patients	116	55	
# Events	226	96	
Rate per patient-year of follow-up ^a (95% Two-sided Conf Int)	0.83 (0.73, 0.94)	0.43 (0.35, 0.52)	< 0.0001

^a p-value and confidence interval are obtained from a Poisson regression model

MR severity at baseline and follow up in patients with paired data at baseline and follow-up are summarized in Table 77. At discharge, MR is reduced in a majority of patients (89.8%) to $\leq 2+$ and in 54.9% of patients to $\leq 1+$. Among patients with paired data at baseline and 1 year, MR reduction was sustained to $\leq 2+$ in 85.4% of patients and to $\leq 1+$ in 38.6% of patients.

**Table 88: REALISM HR Arm - MR Grade at Baseline and Follow-up
Patients with Paired Data at Baseline and Follow-up**

MR Severity	Baseline % (n/N)	Discharge % (n/N)	Baseline % (n/N)	12 Months % (n/N)
0 : None	0.0% (0/255)	0.4% (1/255)	0.0% (0/171)	1.2% (2/171)
1+: Mild	1.2% (3/255)	54.5% (139/255)	0.6% (1/171)	37.4% (64/171)
2+: Moderate	10.2% (26/255)	34.9% (89/255)	17.5% (30/171)	46.8% (80/171)
3+: Moderate-to-severe	56.5% (144/255)	8.6% (22/255)	56.1% (96/171)	11.1% (19/171)
4+: Severe	32.2% (82/255)	1.6% (4/255)	25.7% (44/171)	3.5% (6/171)

Freedom from the combined endpoint of death and MR $>2+$ at 1 year was 64.7% for the REALISM HR patients. Freedom from the combined endpoint of death and MR $>1+$ at 1 year was 38.6% for the REALISM HR patients.

Appendix G Integrated High Surgical Risk Cohort

G1. INTEGRATED HIGH SURGICAL RISK COHORT – STUDY COMPLIANCE

Visit compliance in the Integrated HSR Cohort was high (> 97%) through 2 years (Table 89). Clinical follow-up occurred in 93.2% of patients at 1 year and in 92.4% at 2 years.

Table 89: Integrated HSR Cohort – Study Compliance

Follow-up Visit	# Visits	# Missed Visit	# Deaths before visit	# Withdrawn before visit	Not Due for Visit	Visit Compliance	Clinical Follow-up Occurred In
30-Day	324	4	18	5	0	98.8%	97.4%
1-Year	247	8	80	16	0	97.6%	93.2%
2 Years	122	2	73	14	140	99.0%	92.4%
3 Years	39	1	31	7	273	98.6%	89.7%

G2. INTEGRATED HIGH SURGICAL RISK COHORT - HIGH SURGICAL RISK CHARACTERISTICS

One hundred fifty-one (151) of the 351 patients were included based on STS mortality risk \geq 12%. The remaining 200 (56.9%) were considered high surgical risk due to one or more of the pre-specified surgical risk factors, as shown in (Table 90) and the determination by a cardiac surgeon that the patient was too high risk for mitral valve surgery.

Table 90: Integrated HSR Cohort - Patients with Pre-specified Surgical Risk Factors (STS Mortality Risk <12%)

Pre-Specified Surgical Risk Factor ^a	Integrated HSR Cohort (N=200)
Functional MR with LVEF < 40%	52.0% (104/200)
Re-operation with patent grafts	49.0% (98/200)
Two or more prior chest surgeries	20.5% (41/200)
Over 75 years old with LVEF < 40%	25.5% (51/200)
Three or more STS high risk factors ^b	8.0% (16/200)
Hepatic cirrhosis	3.0% (6/200)
Porcelain aorta or mobile ascending aortic atheroma	3.5% (7/200)
Post-radiation mediastinum	4.0% (8/200)
Previous mediastinitis	0.5% (1/200)

^a Patients may be included in more than one category

^b Creatinine > 2.5 mg/dL, prior chest surgery, age over 75, EF < 35%

G3. INTEGRATED HIGH SURGICAL RISK COHORT – ADDITIONAL EFFECTIVENESS RESULTS

Freedom from the composite of death and MR > 2+ and freedom from the composite of death and MR > 1+ were evaluated by fitting a Weibull distribution to the data. Freedom from death and MR > 2+ and freedom from death and MR > 2+ were 62.6% and 29.5% at 1 year (Figure 19 and Figure 20).

Figure 19: Integrated HSR Cohort (N = 351) - Weibull Freedom from Death and MR > 2+

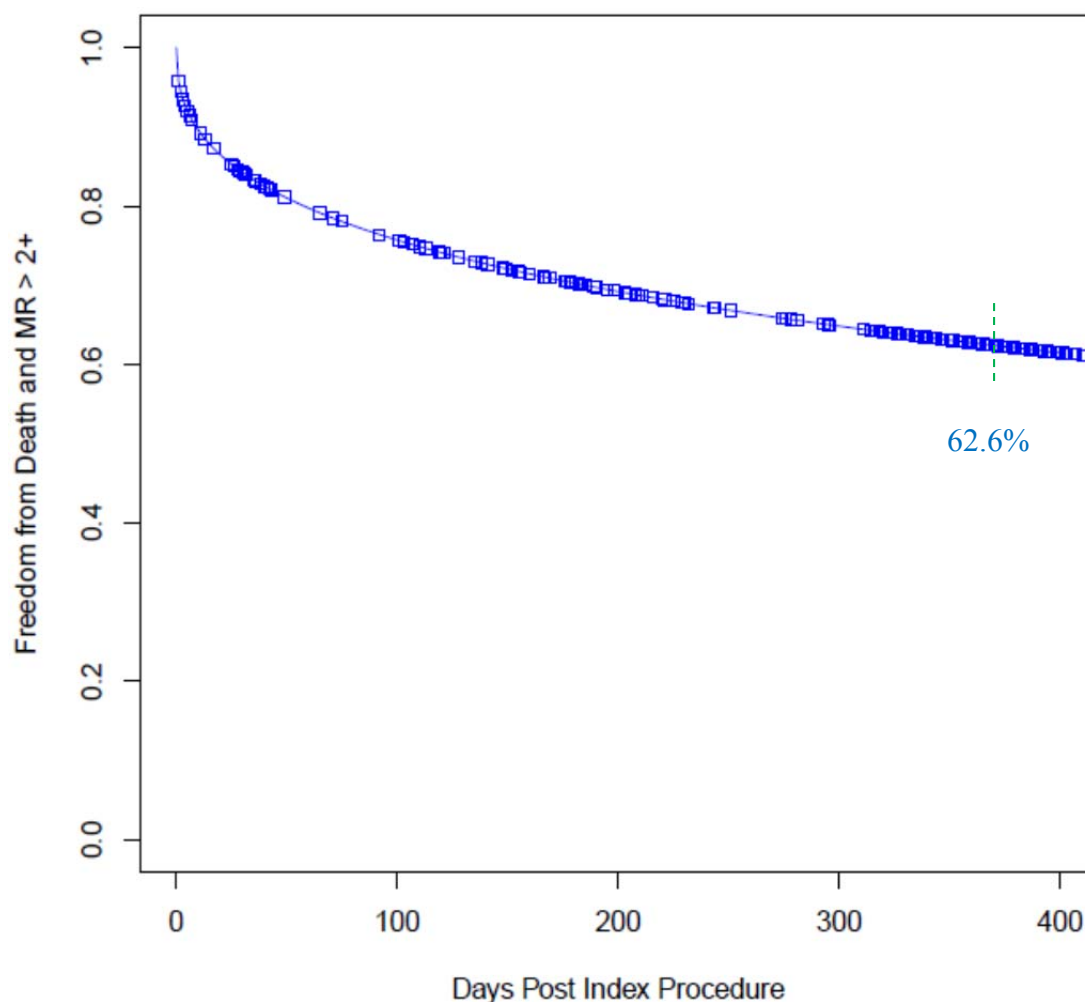
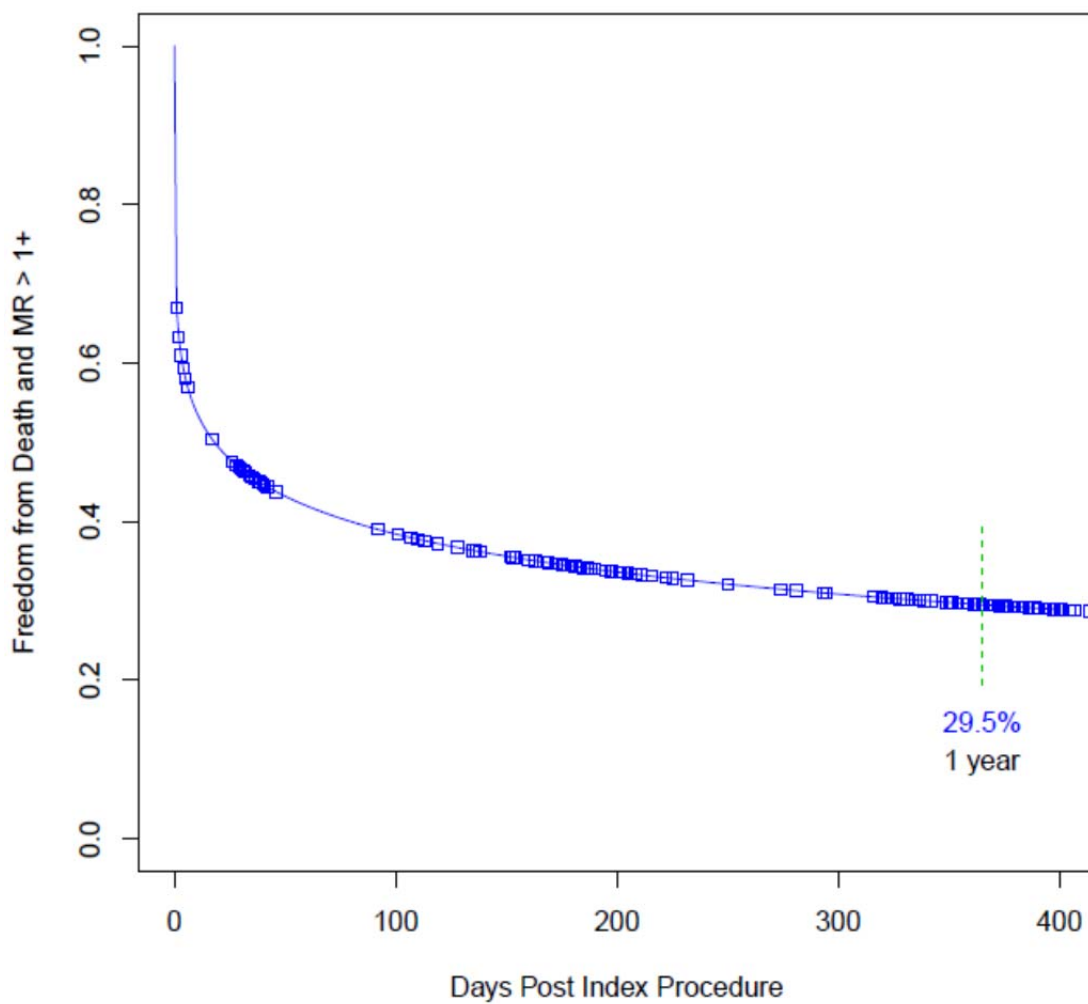


Figure 20: Integrated HSR Cohort (N = 351) - Weibull Freedom from Death and MR > 1+



Appendix H Report on Duke University Medical Center Cardiac Database

H1. PURPOSE

The purpose of this report is to compare 30-day and 12-month survival in the 211 MitraClip Propensity Score Analysis Cohort (MitraClip PSA Cohort) to a historical matched cohort of high surgical risk patients with a diagnosis of moderate-to-severe (3+) or severe (4+) MR who were managed non-surgically at Duke University Medical Center.

H2. METHODS

Data from Duke were obtained by merging from multiple sources at Duke.

H2.1 Data Sources at Duke University Medical Center

The primary source for echocardiographic procedural details was the Duke Echocardiography Laboratory. These data were collected as part of routine patient care at Duke Medical Center.

Data has also been prospectively entered into the DDCD since 1969 and includes demographic, clinical history and physical examination information, along with catheterization and surgery details on all patients undergoing cardiac catheterization or cardiac surgery at the Duke University Medical Center. These data were linked with laboratory, in-subject medication data, and admission and discharge information available in Duke Hospital administrative sources.

Administrative hospital source data repositories were also available and included the Data Support Repository (DSR) and the SASFY (admission and discharge data). Included in these datasets were discharge diagnosis codes and procedural codes.

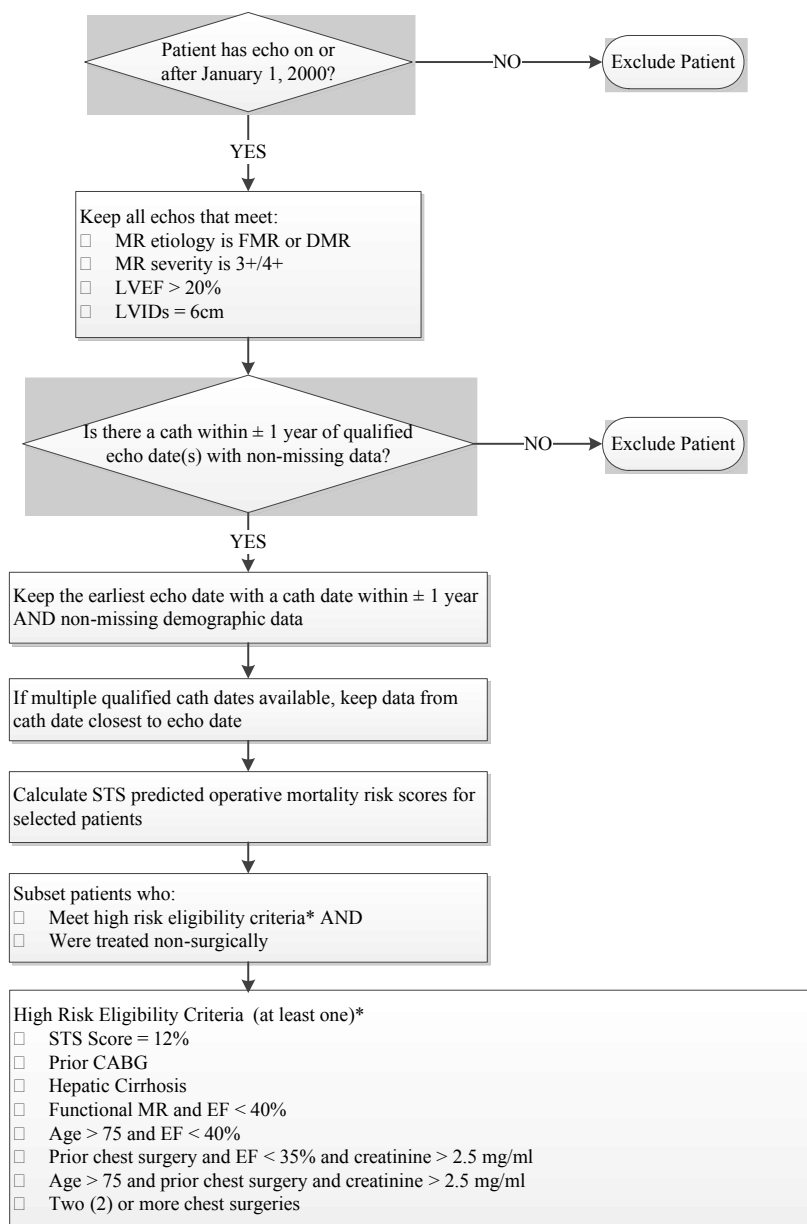
All patients who underwent cardiac catheterization in the DDCD were followed at 6 months, 1 year, and annually thereafter to obtain vital status, hospitalizations (including indications), and medication usage. Patients who did not respond to mailed questionnaires or telephone follow-up were researched in the National Death Index (NDI Plus) and Social Security Death Index (SSDI) to obtain vital status and cause of death information.

Approximately 86,000 cardiac catheterization procedures were performed between 1995 and August 2010, representing roughly 50,000 unique subjects. Detailed clinical data from these procedures were available for merging with echocardiographic data and outcome assessments.

H2.2 Patient Selection

The process flow listed in Figure 21 was used to identify high surgical risk patients from Duke with 3+ or 4+ MR who were managed non-surgically. The EVEREST II HRR study began enrollment in 2006. In order to ensure a contemporaneous cohort of patients for matching, Abbott Vascular's (AV) clinical consultants recommended limiting the Duke Database patients to the years 2000-2010. Surgical risk status of patients from Duke was determined using the definition of high surgical risk as outlined in the protocol for the EVEREST II HRR. STS scores were calculated programmatically for the patients in the Duke Cohort and validated against the STS online calculator.

Figure 21: Duke Database Patient Selection Work Flow



Nine hundred and fifty three (953) patients who were managed non-surgically were identified as high surgical risk in the Duke Database (Duke Cohort), and were potential candidates for matching to the 211 MitraClip PSA Cohort.

The baseline and demographic characteristics of the Duke Cohort are summarized and compared to the MitraClip PSA Cohort in Table 91. Like the MitraClip PSA Cohort, the Duke Cohort patients managed non-surgically had a large number of co-morbidities at baseline. Similar proportions of patients in the MitraClip PSA Cohort and Duke Cohort had a history of MI (48.8% vs. 42.8%), stroke (14.2% vs. 14.7%), and COPD (12.3% vs. 7.1%). Large proportions of patients in the MitraClip PSA Cohort and Duke Cohort had previous cardiac surgery, 58.3% and 49.9%, respectively. Diabetes was prevalent in the two groups, 40.3% in the MitraClip PSA Cohort and 35.5% in the Duke Cohort. Left ventricular internal diameter in systole (LVIDs) was comparable between the two cohorts at 4.2 cm.

However, there were some important differences between patients in the Duke Cohort and the MitraClip PSA Cohort. MitraClip PSA Cohort patients were older on average by seven (7) years than Duke Cohort patients. MitraClip PSA Cohort patients were also nearly twice as likely to be classified as NYHA Functional Class III/IV at baseline, than the Duke Cohort patients, 85.8% vs. 46.6%, respectively. Mitral regurgitation was primarily of functional etiology in patients in the Duke Cohort. Likely as a consequence of this, the average LVEF in the Duke Cohort was 36.7% compared to 49.2% in the MitraClip PSA Cohort.

These differences in important baseline and demographic characteristics (age, NYHA Functional Class III/IV, LVEF, and MR etiology) necessitate matching in order to make meaningful comparisons of survival between the two cohorts.

**Table 91: Demographic and Baseline Characteristics
MitraClip PSA Cohort and Duke Cohorts**

Characteristic	MitraClip PSA Cohort (N = 211)	Duke Cohort (N = 953)
Age, years		
Mean ± SD (N)	76.0 ± 10.3 (211)	68.5 ± 13.2 (953)
Patients over 75 years of age, % (n/N)	57.3% (121/211)	36.1% (344/953)
Male Gender, % (n/N)	60.7% (128/211)	48.9% (466/953)
Body Mass Index (kg/m ²)		
Mean ± SD (N)	26.2 ± 5.6 (211)	27.1 ± 6.2 (953)
Previous Cardiac Surgery, % (n/N)	58.3% (123/211)	49.9% (476/953)
Myocardial infarction, % (n/N)	48.8% (102/209)	42.8% (408/953)
NYHA III/IV, % (n/N)	85.8% (181/211)	46.6% (440/944)
COPD ^a , % (n/N)	12.3% (26/211)	7.1% (68/953)
Atrial Fibrillation, % (n/N)	63.6% (124/195)	51.7% (493/953)
Stroke, % (n/N)	14.2% (30/211)	14.7% (140/953)
Diabetes, % (n/N)	40.3% (85/211)	35.5% (338/953)
Renal Disease, % (n/N)	30.8% (65/211)	18.5% (176/953)
Functional MR Etiology, % (n/N)	70.6% (149/211)	93.2% (888/953)
LV Ejection Fraction, %		
Mean ± SD (N)	49.2 ± 13.7 (201)	36.7 ± 10.9 (953)
LV Internal Diameter, systole (cm)		
Mean ± SD (N)	4.2 ± 1.1 (201)	4.2 ± 1.0 (953)
STS Predicted Operative Mortality Score	12.2 ± 7.9 (211)	9.7 ± 8.8 (953)

^a COPD was defined as dyspneic with the use of home O₂

H2.3 Statistical Analysis

All analyses were pre-specified in a Statistical Analysis Plan (SAP) that was developed in collaboration with clinical experts and statisticians. The SAP was reviewed and approved by statisticians at Duke University, statisticians from Abbott Vascular as well as an independent statistician from Harvard Clinical Research Institute. Analyses were performed by the statisticians at Duke University. The SAP and its amendments are available on file at Abbott Vascular.

H2.3.1 Patient Matching

Propensity score based methods are well accepted means of reducing bias in comparisons between two groups when data are not obtained from a randomized controlled trial. Patient matching was performed using the method of nearest available Mahalanobis distance metric within calipers defined by the propensity score. Three levels of matching were performed:

Matched Cohort 1: As recommended by Rosenbaum and Rubin¹¹, a caliper size of a quarter (0.25) of the (average) standard deviation of the logit of the propensity scores was used. Patients were first matched to within a caliper of 0.25. If multiple matches were identified for a MitraClip PSA Cohort patient, the match was narrowed to a single patient based on the smallest Mahalanobis distance.

Matched Cohort 2: The caliper size was expanded to 0.4 from 0.25 for patients with no matches within the narrower caliper.

Matched Cohort 3: Finally, MitraClip PSA Cohort patients with no matches within the expanded caliper of 0.4 were matched to patients in the Duke Cohort with the nearest propensity score.

Since the degree of imbalance between the two groups in some of the baseline and demographic characteristics such as age, LVEF and NYHA Class III/IV was large, the resulting distributions of the initial propensity scores obtained using data from all 953 patients in the Duke Cohort did not yield sufficient overlap (Figure 28 in Appendix H, Attachment 1). Therefore, data from the Duke Cohort were “trimmed” as follows. Patients in the Duke Cohort with age and/or LVEF outside the range of the corresponding mean \pm 1.5 SD from the MitraClip PSA Cohort were excluded from further consideration. Thus, patients in the Duke Cohort with continuous variable data who were unlikely to be “good matches” to the MitraClip PSA Cohort patients were excluded, resulting in a “trimmed” Duke Cohort (N = 527). Matches for the MitraClip PSA Cohort were then obtained from the Trimmed Duke Cohort.

The clinical variables included in the logistic regression model for generating the propensity scores (Pr[treatment with MitraClip given covariates]) represented important demographic characteristics and baseline co-morbidities that were prevalent in both cohorts, and defined a relatively sick population. The following variables were used in the logistic regression model: age, gender, previous MI, previous stroke, COPD, history of renal disease, diabetes, previous cardiac surgery, NYHA Functional Class III/IV, and LVEF. Many of these variables were also identified to be significant baseline predictors of mortality in the Duke Cohort (Table 100 in Appendix H, Attachment 1). MR etiology was not included in the model because other baseline co-morbidities such as previous MI, lower LVEF and previous cardiac surgery are highly correlated with functional etiology.

H2.4 Demographic and Baseline Characteristics

Categorical variables were summarized as counts and proportions, while continuous variables were summarized using means and standard deviations. Baseline and demographic characteristics between the two groups in the matched cohort were compared using Pearson’s chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables.

H2.5 30-Day and 1-Year Mortality

Duration of follow-up in the Duke Cohort was calculated from the date of echo to the date of death or 365 days post-echo, whichever was shorter. Duration of follow-up in the MitraClip PSA Cohort was calculated from the date of the MitraClip procedure to the date of death or 365 days post-procedure, whichever was shorter. The following pre-specified mortality analyses were performed:

- A Kaplan-Meier analysis in the Duke Cohort
- A Kaplan-Meier analysis in the “Trimmed” Duke Cohort
- Stratified Cox proportional hazards regression models that included the effect of treatment (MitraClip vs. No MitraClip) was employed for the mortality analyses in the following matched patient cohorts. Quartiles of the propensity score were used for stratification to obtain greater precision in the estimation of the hazard ratio.
 - Matched cohort obtained using a caliper size of $0.25 \times \text{SD}$ of the logit of the propensity score (Matched Cohort 1).
 - Matched cohort obtained using an expanded caliper size of $0.4 \times \text{SD}$ of the logit of the propensity score. This cohort contained all patients who were matched within a caliper of $0.25 \times \text{SD}$ of the logit of the propensity score, in addition to patients who are matched with a slight larger caliper size of $0.4 \times \text{SD}$ of the logit of the propensity score (Matched Cohort 2).
 - Analyses of mortality were also performed on the entire cohort of 211 matched patients, where some MitraClip high surgical risk patients were matched to Duke high surgical risk patients with the nearest propensity score outside the caliper size of $0.4 \times \text{SD}$ of the logit of the propensity score. Since matches for some patients were less optimal, these analyses were considered exploratory (Matched Cohort 3).
- The following additional pre-specified exploratory analyses were also performed:
 - Multivariable Cox proportional hazards model in the Trimmed Duke Cohort ($N = 527$) to identify baseline predictors of mortality in patients managed non-surgically. The following variables were included for model selection: age, gender, previous cardiac surgery, history of COPD, history of renal disease, diabetes, previous MI, previous stroke, MR etiology (functional or degenerative), NYHA Class III/IV, LVEF and LVIDs.
 - Since there were a limited number of patients with degenerative MR, a comparative analysis of mortality with stratification for MR etiology as specified in the SAP was not feasible. Instead, a stratified Cox proportional hazards model was used to compare mortality in the functional MR subgroup of Matched Cohort 1.
- Other mortality analyses reported are descriptive.

H3. RESULTS

H3.1 Demographic and Baseline Characteristics

H3.1.1 “Trimmed” Duke Cohort (Without Matching)

As expected, after trimming, the two cohorts were more balanced with respect to age and LVEF (Table 92) than when including all 953 Duke patients. There was little change otherwise in the distribution of the remaining baseline and demographic characteristics.

**Table 92: Demographic and Baseline Characteristics
MitraClip PSA Cohort and “Trimmed” Duke Cohort**

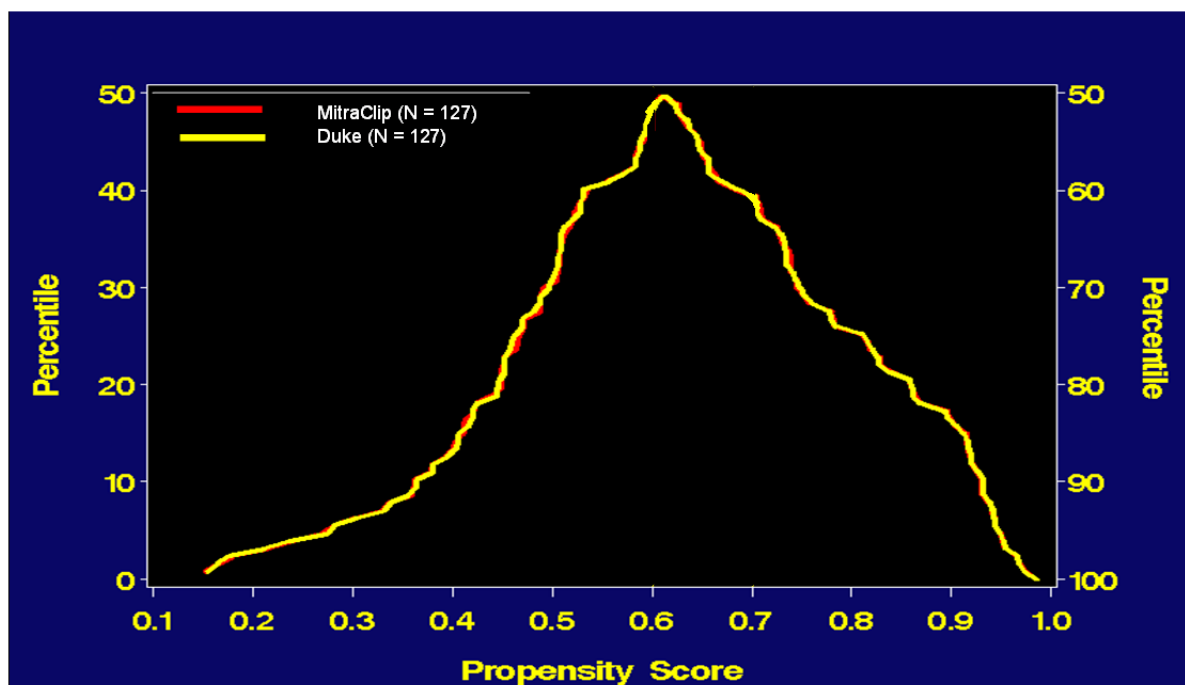
Characteristic	MitraClip PSA Cohort (N = 211)	Trimmed Duke Cohort (N = 527)
Age, years		
Mean ± SD (N)	76.0 ± 10.3 (211)	74.7 ± 7.9 (527)
Patients over 75 years of age, % (n/N)	57.3% (121/211)	50.1% (264/527)
Male Gender, % (n/N)	60.7% (128/211)	46.3% (244/527)
Body Mass Index (kg/m ²)		
Mean ± SD (N)	26.2 ± 5.6 (211)	26.9 ± 5.8 (527)
Previous Cardiac Surgery, % (n/N)	58.3% (123/211)	60.2% (317/527)
Myocardial infarction, % (n/N)	48.8% (102/209)	44.4% (234/527)
NYHA III/IV, % (n/N)	85.8% (181/211)	40.2% (209/520)
COPDa, % (n/N)	12.3% (26/211)	7.2% (38/527)
Atrial Fibrillation, % (n/N)	63.6% (124/195)	57.9% (305/527)
Stroke, % (n/N)	14.2% (30/211)	15.6% (82/527)
Diabetes, % (n/N)	40.3% (85/211)	40.0% (211/527)
Renal Disease, % (n/N)	30.8% (65/211)	20.5% (108/527)
Functional MR Etiology, % (n/N)	70.6% (149/211)	90.5% (477/527)
LV Ejection Fraction, %		
Mean ± SD (N)	49.2 ± 13.7 (201)	41.7 ± 9.6 (527)
LV Internal Diameter, systole (cm)		
Mean ± SD (N)	4.2 ± 1.1 (201)	3.9 ± 0.9 (527)
STS Predicted Operative Mortality Score	12.2 ± 7.9 (211)	11.5 ± 8.9 (527)

^a COPD was defined as dyspneic with the use of home O₂

H3.1.2 Matched Cohort 1 – Caliper Width of 0.25

Matched Cohort 1 was derived using the narrowest caliper size of 0.25*SD of the logit of the propensity score. One hundred and twenty seven (127) of the 211 MitraClip PSA Cohort patients were matched 1:1 to patients in the Trimmed Duke Cohort. Figure 22 is a mountain plot of the propensity scores in the matched cohort of MitraClip and Duke patients. The figure shows a high degree of overlap in the (empirical cumulative) distributions of the propensity scores of the two groups. The high degree of overlap in propensity scores also resulted in comparable baseline and demographic characteristics between the two groups in Matched Cohort 1 (Table 93).

Figure 22: Mountain Plot of Propensity Scores in Matched Cohort 1



Baseline and demographic characteristics of the two groups in Matched Cohort 1 are summarized in Table 93. Both groups were elderly with an average age of approximately 75 years. Both groups had a large number of baseline co-morbidities including previous cardiac surgery, previous MI, a history of COPD, renal disease and diabetes. These baseline co-morbidities were equally prevalent at high rates in the two groups, with no statistically significant differences. Mean LVIDs was statistically significantly different between the two groups with a mean diameter of 4.5 cm for Cohort 1 MitraClip patients and 3.9 cm for Cohort 1 Duke patients. Since prognosis has been reported to be worse with LVIDs larger than 4.0cm⁴, mortality comparisons between the two groups in the matched cohort are likely to be conservatively biased against the MitraClip.

The differences which were notable previously with respect to NYHA Functional Class, LVEF and MR etiology between the two groups with the Duke Cohort (N = 953), and the Trimmed Duke Cohort (N = 527) were no longer significant after matching. After matching, MR etiology was primarily functional in the MitraClip and Duke Cohorts, 84.3% and 88.2% respectively. In Matched Cohort 1, Duke patients had an average LVEF of 44.1% which was similar to the MitraClip patients whose average LVEF was 43.0%.

The proportions of patients classified as NYHA Functional Class III/IV were also comparable in the two groups (78.0% of MitraClip patients and 74.8% of Duke patients). Thus, the

matched cohort of 127 MitraClip high surgical risk patients and 127 Duke high surgical risk patients were comparable with respect to all important baseline and demographic characteristics, allowing for meaningful formal comparisons of survival based on therapy received.

Five additional patient matches were obtained with the expanded caliper width. Even with the slightly expanded caliper width, matches were close. As with the caliper width of 0.25, there were no statistically significant differences in baseline and demographic characteristics with the exception of mean LVIDs. The results for Matched Cohort 2 were consistent with Matched Cohort 1 and are not included in this report.

**Table 93: Demographic and Baseline Characteristics
Matched Cohort 1 (Caliper Size = 0.25)**

Characteristic	MitraClip (N = 127)	Duke (N = 127)	p-value
Age, years			
Mean \pm SD (N)	74.6 \pm 10.5 (127)	74.6 \pm 7.9 (127)	0.547
Patients over 75 years of age, % (n/N)	52.8% (67/127)	51.2% (65/127)	0.802
Male Gender, % (n/N)	52.8% (67/127)	51.2% (65/127)	0.802
Body Mass Index (kg/m ²)			
Mean \pm SD (N)	26.2 \pm 4.8 (127)	27.2 \pm 5.2 (127)	0.093
Previous Cardiac Surgery, % (n/N)	55.1% (70/127)	52.8% (67/127)	0.706
Myocardial infarction, % (n/N)	44.4% (56/126)	44.9% (57/127)	0.944
NYHA III/IV, % (n/N)	78.0% (99/127)	74.8% (95/127)	0.555
COPDa, % (n/N)	9.4% (12/127)	5.5% (7/127)	0.233
Atrial Fibrillation, % (n/N)	56.5% (65/115)	61.4% (78/127)	0.439
Stroke, % (n/N)	14.2% (18/127)	8.7% (11/127)	0.167
Diabetes, % (n/N)	44.9% (57/127)	37.0% (47/127)	0.202
Renal Disease, % (n/N)	28.3% (36/127)	26.0% (33/127)	0.672
Functional MR Etiology, % (n/N)	84.3% (107/127)	88.2% (112/127)	0.363
LV Ejection Fraction, %			
Mean \pm SD (N)	43.0 \pm 11.8 (120)	44.1 \pm 9.8 (127)	0.351
LV Internal Diameter, systole (cm)			
Mean \pm SD (N)	4.5 \pm 1.0 (121)	3.9 \pm 1.0 (127)	< 0.0001
STS Predicted Operative Mortality Score	11.1 \pm 7.1 (127)	13.2 \pm 10.7 (127)	0.322

^a COPD was defined as dyspneic with the use of home O₂

H3.1.3 Matched Cohort 3 – Caliper Width of 0.25, 0.4 or Nearest Propensity Score

Table 94 summarizes the demographic and baseline characteristics of the 211 MitraClip PSA Cohort patients and their matches in the Duke Cohort. The two groups were well balanced with respect to most baseline and demographic characteristics. However, since matches were obtained outside a caliper of 0.25 for 84 (=211 - 127) patients, some variables (MR etiology, LVEF and LVIDs) were statistically significantly different.

**Table 94: Demographic and Baseline Characteristics
Matched Cohort 3 (Caliper Size = 0.25, 0.4 or Nearest Propensity Score)**

Characteristic	MitraClip (N = 211)	Duke (N = 211)	p-value
Age, years			
Mean ± SD (N)	76.0±10.3 (211)	75.1±7.8(211)	0.073
Patients over 75 years of age, % (n/N)	57.3% (121/211)	52.1% (110/211)	0.282
Male Gender, % (n/N)	60.7% (128/211)	54.0% (114/211)	0.168
Body Mass Index (kg/m ²)			
Mean ± SD (N)	26.2±5.6 (211)	27.4±5.9 (211)	0.028
Previous Cardiac Surgery, % (n/N)	58.3% (123/211)	55.9% (118/211)	0.623
Myocardial infarction, % (n/N)	48.8% (102/209)	41.7% (88/211)	0.144
NYHA III/IV, % (n/N)	85.8% (181/211)	79.6% (168/211)	0.094
COPD ^a , % (n/N)	12.3% (26/211)	9.5% (20/211)	0.349
Atrial Fibrillation, % (n/N)	63.6% (124/195)	64.0% (135/211)	0.935
Stroke, % (n/N)	14.2% (30/211)	13.7% (29/211)	0.888
Diabetes, % (n/N)	40.3% (85/211)	42.2% (89/211)	0.692
Renal Disease, % (n/N)	30.8% (65/211)	23.2% (49/211)	0.079
Functional MR Etiology, % (n/N)	70.6% (149/211)	90.0% (190/211)	<0.0001
LV Ejection Fraction, %			
Mean ± SD (N)	49.2±13.7 (201)	43.6±9.8 (211)	<0.0001
LV Internal Diameter, systole (cm)			
Mean ± SD (N)	4.2±1.1 (201)	3.9±1.0 (211)	0.0005
STS Predicted Operative Mortality Score	12.2±7.9 (211)	12.9±9.5(211)	0.801

^a COPD was defined as dyspneic with the use of home O₂

H3.1.4 Functional MR Subgroup from Matched Cohort 1

Table 95 summarizes and compares demographic and baseline characteristics of FMR patients between the two groups in Matched Cohort 1. Diabetes was more prevalent in Cohort 1 MitraClip FMR patients (46.7%) than in the Cohort 1 Duke FMR patients (35.7%). Cohort 1 MitraClip FMR patients were also classified as NYHA Functional Class III/IV at a higher rate (81.3%) than Cohort 1 Duke FMR patients (73.2%). These differences however were not statistically significant. The difference in mean LVIDs was statistically significant ($p < 0.0001$) with the Cohort 1 MitraClip FMR patients presenting with a larger average than the Cohort 1 Duke FMR patients, 4.7 cm vs. 4.0 cm, respectively. The difference in mean BMI was marginally non-significant ($p = 0.057$), the Cohort 1 Duke FMR patients had a slightly higher average BMI than the Cohort 1 MitraClip FMR patients. The two groups of FMR patients were generally comparable, with most of the larger differences in baseline co-morbidities biased conservatively against the MitraClip.

**Table 95: Demographic and Baseline Characteristics
FMR Subgroup from Matched Cohort 1 (Caliper Size = 0.25)**

Characteristic	MitraClip FMR (N = 107)	Duke FMR (N = 112)	p-value
Age, years			
Mean ± SD (N)	73.0±10.4 (107)	73.9±7.6 (112)	0.844
Patients over 75 years of age, % (n/N)	45.8% (49/107)	48.2% (54/112)	0.720
Male Gender, % (n/N)	52.3% (56/107)	52.7% (59/112)	0.960
Body Mass Index (kg/m ²)			
Mean ± SD (N)	26.1±4.9 (107)	27.3±5.1 (112)	0.057
Previous Cardiac Surgery, % (n/N)	55.1% (59/107)	53.6% (60/112)	0.816
Myocardial infarction, % (n/N)	49.1% (52/106)	47.3% (53/112)	0.798
NYHA III/IV, % (n/N)	81.3% (87/107)	73.2% (82/112)	0.154
COPD ^a , % (n/N)	9.3% (10/107)	6.3% (7/112)	0.392
Atrial Fibrillation, % (n/N)	56.7% (55/97)	60.7% (68/112)	0.557
Stroke, % (n/N)	15.9% (17/107)	8.9% (10/112)	0.117
Diabetes, % (n/N)	46.7% (50/107)	35.7% (40/112)	0.098
Renal Disease, % (n/N)	30.8% (33/107)	26.8% (30/112)	0.508
LV Ejection Fraction, %			
Mean ± SD (N)	40.7±10.0 (103)	43.0±9.6 (112)	0.144
LV Internal Diameter, systole (cm)			
Mean ± SD (N)	4.7±0.9 (104)	4.0±0.9 (112)	< 0.0001
STS Predicted Operative Mortality Score	10.9±7.3 (107)	12.9±11.1 (112)	0.526

^a COPD was defined as dyspneic with the use of home O₂

H3.1.5 Unmatched MitraClip PSA Cohort Patients

Since matches were obtained for only 127 of the 211 MitraClip PSA Cohort patients within the caliper of 0.25, it was important to examine the baseline and demographic characteristics of the remaining 84 patients. Table 96 provides a comparison of the 127 MitraClip patients who were in Matched Cohort 1 (using a 0.25 caliper) to the remaining 84 unmatched MitraClip patients. Both the matched and the unmatched groups represent very high surgical risk patients of advanced age with multiple co-morbidities. MitraClip patients without matches in the Trimmed Duke Cohort were older on average by 3 years than patients who were matched. In addition, the majority of comorbidities, including prior cardiac surgery, myocardial infarction, renal disease and COPD, were present to a greater degree in the unmatched than the matched patients, suggesting that the unmatched group represents a sicker population. Nearly all of the patients who remained unmatched had advanced heart failure symptoms (NYHA Class III/IV) compared to the roughly three quarters of patients with advanced heart failure symptoms in Matched Cohort 1. In the unmatched patients, functional and degenerative MR etiologies were equally prevalent, and their LVEF was higher on average.

These findings were not surprising given that the candidate pool for matching in the Duke Cohort (N = 953) was younger on average than the MitraClip PSA Cohort, with lower LVEF on average, a lower rate of NYHA Functional Class III/IV, and a higher rate of functional MR.

**Table 96: Demographic and Baseline Characteristics
Cohort 1 Matched and Unmatched MitraClip Patients**

Characteristic	Matched MitraClip Patients (N = 127)	Unmatched MitraClip Patients (N = 84)
Age, years		
Mean \pm SD (N)	74.6 \pm 10.5 (127)	78.0 \pm 9.7 (84)
Patients over 75 years of age, % (n/N)	52.8% (67/127)	64.3% (54/84)
Male Gender, % (n/N)	52.8% (67/127)	72.6% (61/84)
Body Mass Index (kg/m ²)		
Mean \pm SD (N)	26.2 \pm 4.8 (127)	26.4 \pm 6.7(84)
Previous Cardiac Surgery, % (n/N)	55.1% (70/127)	63.1% (53/84)
Myocardial infarction, % (n/N)	44.4% (56/126)	55.4% (46/83)
NYHA III/IV, % (n/N)	78.0% (99/127)	97.6% (82/84)
COPD ^a , % (n/N)	9.4% (12/127)	16.7% (14/84)
Atrial Fibrillation, % (n/N)	56.5% (65/115)	73.8% (59/80)
Stroke, % (n/N)	14.2% (18/127)	14.3% (12/84)
Diabetes, % (n/N)	44.9% (57/127)	33.3% (28/84)
Renal Disease, % (n/N)	28.3% (36/127)	34.5% (29/84)
Functional MR Etiology, % (n/N)	84.3% (107/127)	50.0% (42/84)
LV Ejection Fraction, %		
Mean \pm SD (N)	43.0 \pm 11.8 (120)	58.4 \pm 11.0 (81)
LV Internal Diameter, systole (cm)		
Mean \pm SD (N)	4.5 \pm 1.0 (121)	3.9 \pm 1.0 (80)
STS Predicted Operative Mortality Score	11.1 \pm 7.1(127)	14.0 \pm 8.6(84)

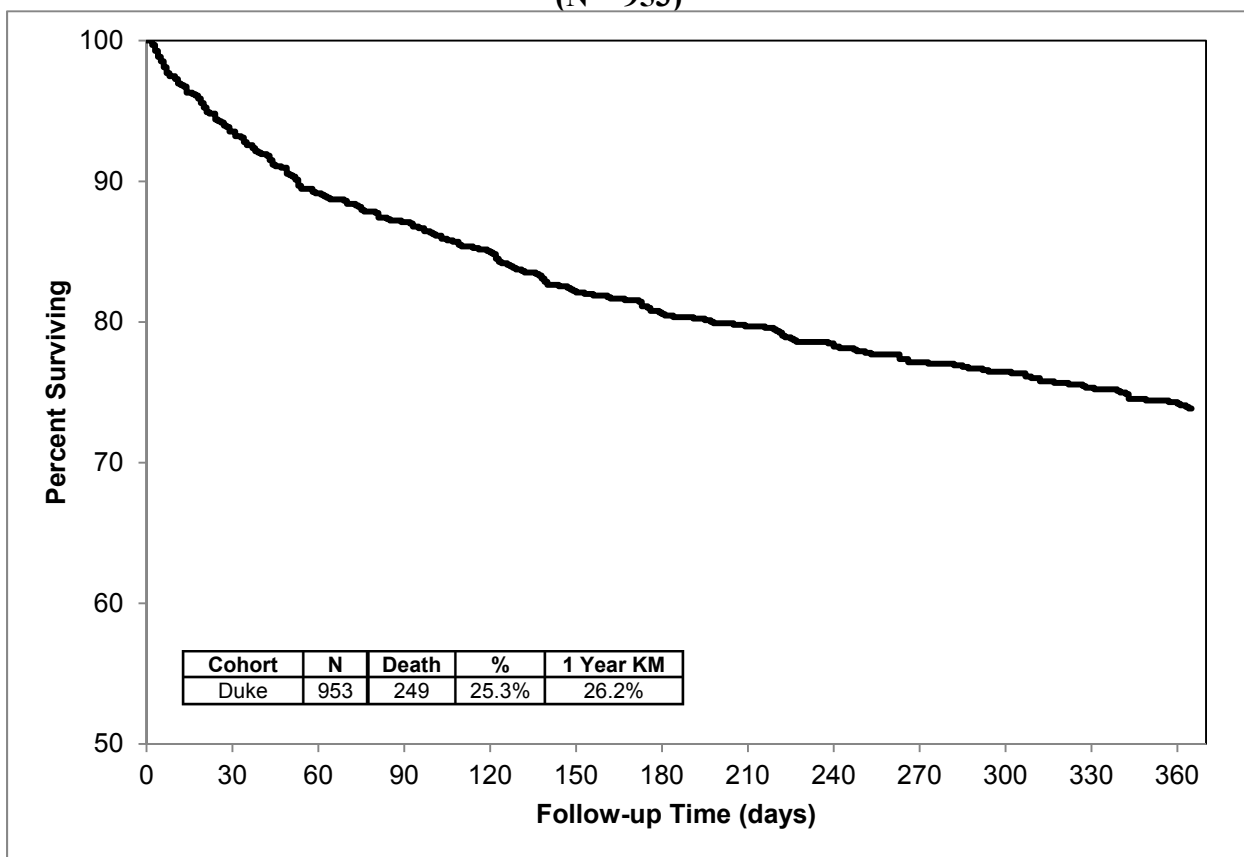
^a COPD was defined as dyspneic with the use of home O₂

H3.2 30-Day and 1-Year Mortality

H3.2.1 Overall Duke Cohort (N = 953)

Figure 23 shows the Kaplan-Meier freedom from all-cause mortality in the overall Duke Cohort of 953 patients. Mortality at 30 days was 6.5%, and mortality at 1 year was 26.2%.

Figure 23: Kaplan-Meier Freedom from All-Cause Mortality, Duke Cohort Patients (N = 953)



H3.2.1.1 Comparison to MitraClip Propensity Score Analysis Cohort

There were some important differences between the Duke Cohort (N = 953) and the MitraClip PSA Cohort (N = 211). As noted earlier, MitraClip PSA Cohort patients were older on average by 7 years than patients in the Duke Cohort. MitraClip PSA Cohort patients were also nearly twice as likely to be classified as NYHA Functional Class III/IV at baseline, than their counterparts in the Duke Cohort. Comparison of mortality between the Duke Cohort and the MitraClip PSA Cohort patients is therefore conservatively biased against the MitraClip.

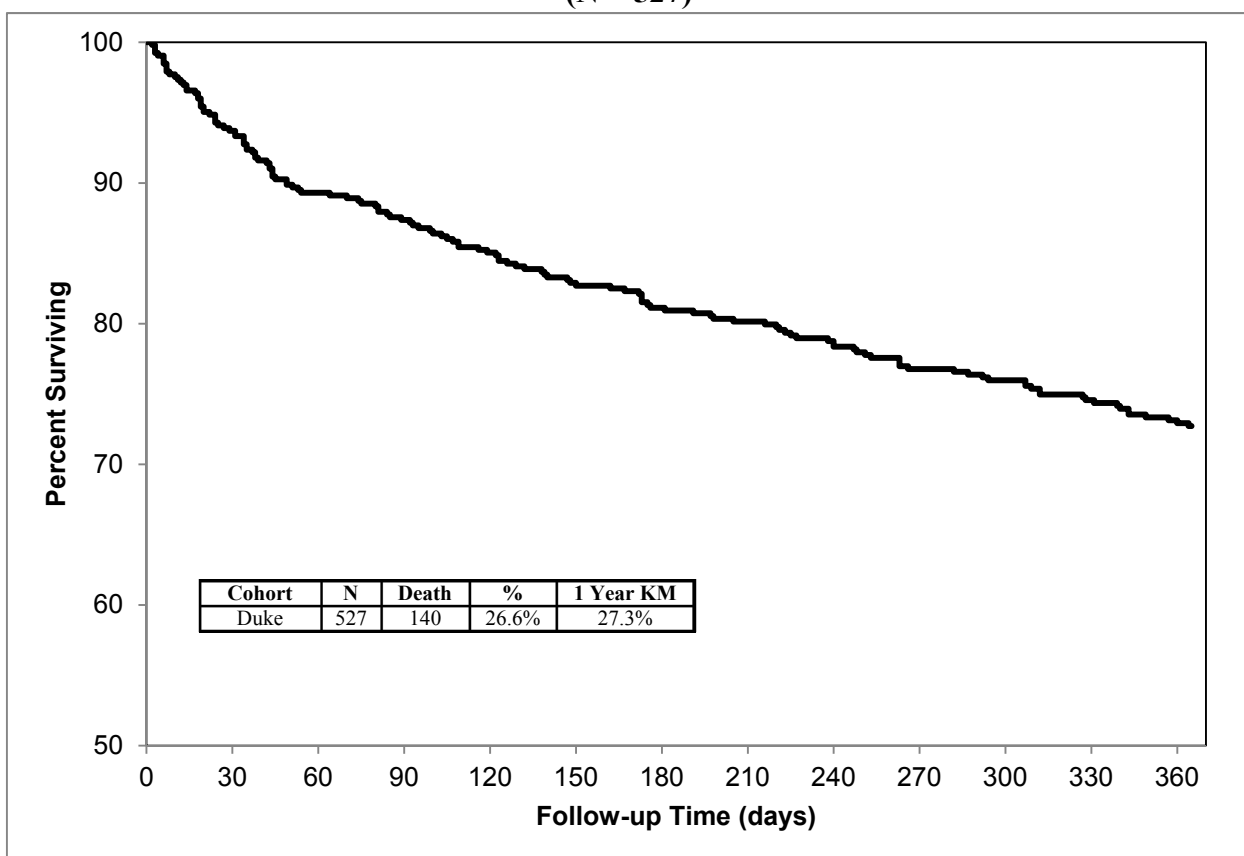
Mortality at 30 days in the MitraClip PSA Cohort patients (N = 211) was 5.3%, which was comparable to the 6.5% observed in Duke Cohort patients. At 1 year, mortality in the MitraClip PSA Cohort patients was 24.1%, again comparable to the 26.2% observed in Duke Cohort patients.

Thus, in a conservative descriptive analysis without patient matching, mortality at 30 days post-procedure and longer term at 1 year in the MitraClip PSA Cohort patients was not worse than that observed in a historical cohort of younger and less sick high surgical risk patients from Duke University Medical Center who were managed non-surgically.

H3.2.2 “Trimmed” Duke Cohort (N = 527)

Figure 24 shows the Kaplan-Meier freedom from all-cause mortality in the Trimmed Duke Cohort.

Figure 24: Kaplan-Meier Freedom from All-Cause Mortality, Trimmed Duke Cohort (N = 527)



H3.2.2.1 Comparison to Literature

The mortality estimates at 30 days was 6.3%, and at 1 year was 27.3% in the Trimmed Duke Cohort. These estimates were in line with mortality reported in the literature in patients with MR managed non-surgically.

H3.2.2.1 Comparison to MitraClip Propensity Score Analysis Cohort

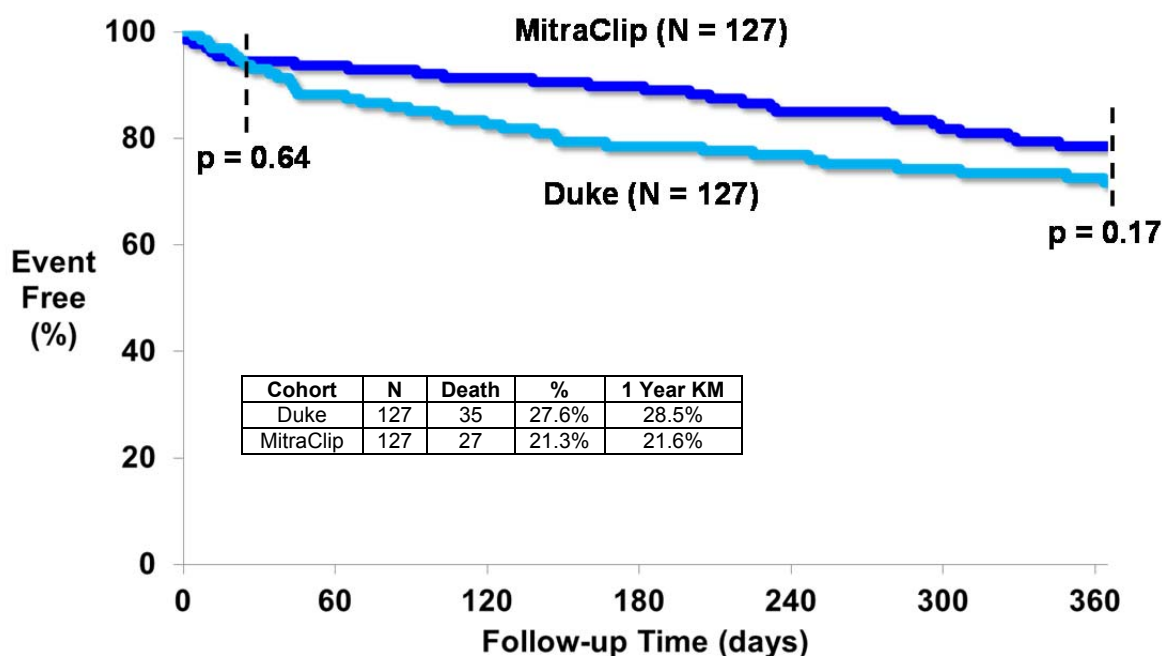
Patients in the Trimmed Duke Cohort were more comparable to MitraClip PSA Cohort patients, at least with respect to age and LVEF, although the difference in the rate of NYHA Class III/IV persisted. Mortality at 30 days post-procedure, and longer term at 1 year in MitraClip PSA Cohort patients treated with the MitraClip was not excessive when compared to that observed in patients in the Trimmed Duke Cohort who were a closer match with respect to age and LVEF (5.3% vs. 6.3% at 30 days; 24.1% vs. 27.3% at 1 year, MitraClip vs. Duke, respectively).

H3.2.3 Matched Cohort 1 (N = 127 per Group)

As described earlier, in Matched Cohort 1, patients treated with the MitraClip were comparable to patients managed non-surgically with respect to all demographic and baseline characteristics, except one. For all measures except LVIDs, differences between the two groups were small and not statistically significant. Patients treated with the MitraClip had a slightly higher mean LVIDs that was statistically significantly different in comparison to patients managed non-surgically. As described earlier, the prognosis in patients with higher LVIDs is generally expected to be worse.

Figure 25 shows the Kaplan-Meier freedom from all-cause mortality in the two groups in Matched Cohort 1. There was no significant difference in 30-day mortality rates between the Cohort 1 MitraClip and Duke patients ($p = 0.64$). The 1-year mortality in the matched Cohort 1 MitraClip and Duke patients were 21.6% and 28.5% respectively. The hazard ratio of all-cause mortality at 1 year of MitraClip to No MitraClip was 0.70 (95% CI: [0.43, 1.17]), i.e., there was a 42% increased hazard of all-cause mortality at 1 year in the Cohort 1 Duke patients over the Cohort 1 MitraClip patients. Thus, the relative risk reduction in mortality due to the MitraClip was estimated to be 30% ($p = 0.172$).

Figure 25: Kaplan-Meier Freedom from All-Cause Mortality, Matched Cohort 1 (N = 127 per Group)



An adjusted analysis of all-cause mortality was performed where baseline LVIDs was included as a covariate in the Cox model in addition to treatment received. Table 97 provides estimates of the hazard ratio from the adjusted Cox model. Baseline LVIDs was significantly associated with all-cause mortality ($p = 0.031$). The hazard of all-cause death increases by 35% with a centimeter increase in the LVIDs. After adjusting for baseline LVIDs, the estimated MitraClip device effect was larger (HR of 0.59; 95% CI: [0.34, 1.00]), i.e., after adjusting for baseline LVIDs, there was a 71% increase in the hazard of all-cause death at 12 months in the Duke patients over the MitraClip patients. This result approached statistical significance with a p -value of 0.049. Therefore, the estimated relative risk reduction in all-cause mortality with the MitraClip at 1 year, after adjustment for baseline LVIDs, was 41%.

**Table 97: Estimates from the Cox Model Adjusted for Baseline LVIDs
Matched Cohort 1**

Effect	Hazard Ratio	p-value	95% Conf Int
LVIDs (cm)	1.35	0.031	(1.03,1.78)
MitraClip	0.59	0.049	(0.34,1.0)

H3.2.4 Matched Cohort 3

Matched Cohort 3 was obtained by matching the 211 patients in the MitraClip PSA Cohort, 1-1, to patients in the Duke Cohort. In addition to the patients who were matched to within a caliper of size 0.25 or 0.4, Matched Cohort 3 contained MitraClip patients who were matched to Duke patients with the nearest propensity score. As described earlier, the differences in MR etiology, LVEF and LVIDs between the two groups in Matched Cohort 3 were statistically significant. Matches remained close with respect to the remaining characteristics. Therefore, the mortality analysis performed only adjusted for MR etiology, LVEF and LVIDs.

After adjustment for MR etiology, LVEF and LVIDs, the hazard ratio of all-cause mortality at 12 months of the MitraClip Cohort over the Duke Cohort was similar to the estimate obtained for Matched Cohort 1 (Table 98). Thus, regardless of the caliper size used for matching, the relative risk reduction in all-cause mortality due to the MitraClip was estimated to be ~30%.

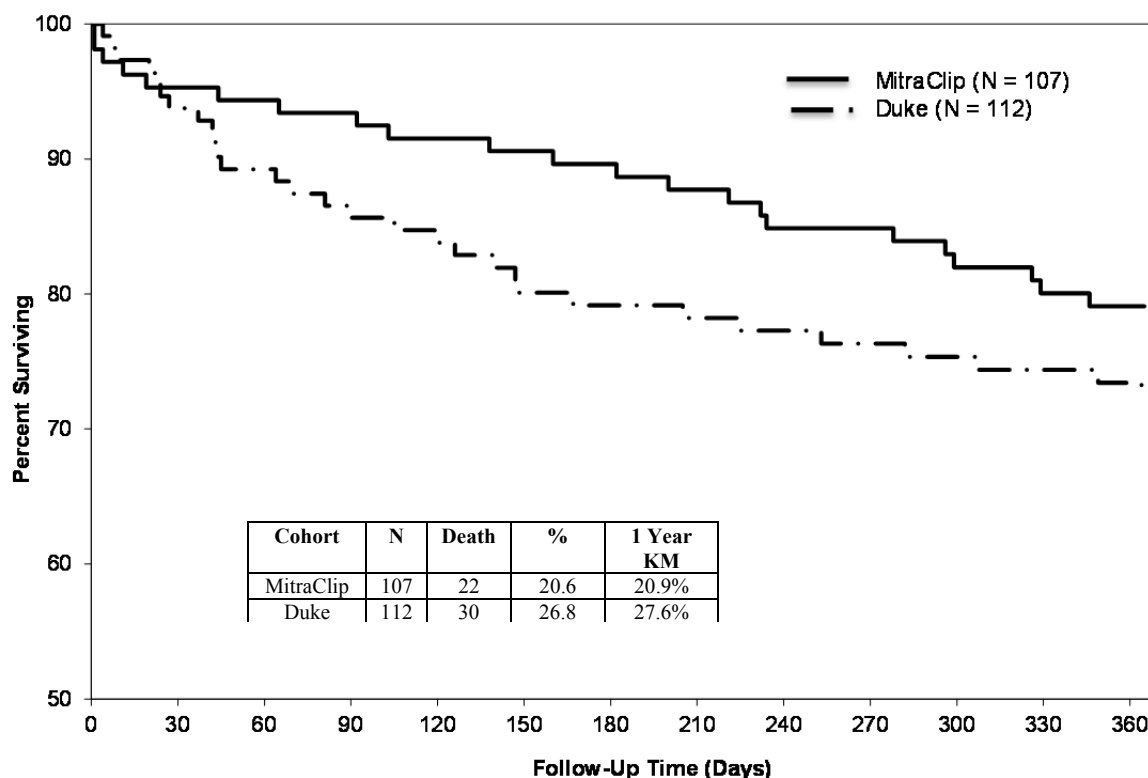
**Table 98: Estimates from the Cox Model Adjusted for baseline LVIDs, LVEF and MR
Etiology, Matched Cohort 3**

Effect	HR (95% CI)	p-value
Degenerative MR	1.45 (0.84, 2.49)	0.183
LVIDs (cm)	1.07 (0.83, 1.38)	0.607
LVEF (%)	0.99 (0.97, 1.01)	0.389
MitraClip	0.69 (0.46, 1.04)	0.080

H3.2.5 Functional MR Subgroup from Matched Cohort 1

Mortality outcomes in the FMR subgroup from Matched Cohort 1 were consistent with the outcomes for the overall cohort. Figure 26 shows Kaplan-Meier freedom from all-cause mortality in FMR patients from Matched Cohort 1.

Figure 26: Kaplan-Meier Freedom from All-Cause Mortality, FMR Subgroup of Matched Cohort 1



Mortality at 30 days in Cohort 1 MitraClip FMR patients was 4.7% compared to 6.3% for Cohort 1 Duke FMR patients. The 1-year mortality in the FMR subgroup of the matched MitraClip and Duke cohorts were 20.9% and 27.6% respectively. The hazard ratio of all-cause mortality at 12 months of MitraClip to No MitraClip was 0.70 (95% CI: [0.40, 1.21]), and the relative risk reduction in all-cause mortality was estimated to be 30% (p = 0.201).

An adjusted analysis of all-cause mortality was performed where baseline LVIDs was included as a covariate in the Cox model in addition to treatment received. Table 99 provides estimates of the hazard ratio from the adjusted Cox model in FMR patients. Baseline LVIDs was more significantly associated with all-cause mortality in the FMR subgroup than in the overall matched cohort. In FMR patients, the hazard of all-cause death increases by 68% with a centimeter increase in the baseline LVIDs. After adjusting for baseline LVIDs, the estimated MitraClip device effect in FMR patients was larger (HR of 0.48; 95% CI: [0.27, 0.88]), and statistically significant with a p-value of 0.017.

**Table 99: Estimates from the Cox Model Adjusted for baseline LVIDs
FMR Subgroup from Matched Cohort 1**

Effect	Hazard Ratio	p-value	95% Conf Int
LVIDs (cm)	1.68	0.002	(1.21, 2.33)
MitraClip	0.48	0.017	(0.27, 0.88)

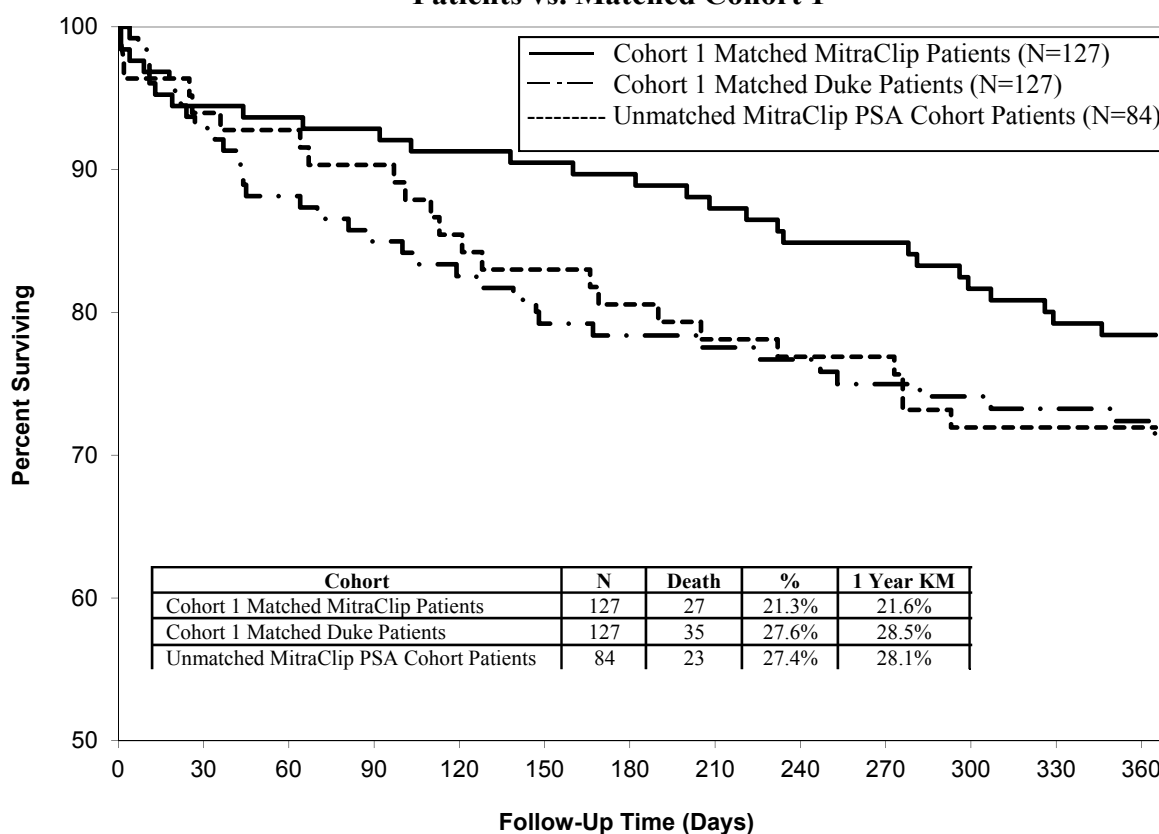
H3.2.6 Unmatched MitraClip Propensity Score Analysis Patients

Since Matched Cohort 3 contained MitraClip PSA Cohort patients for whom matching was less optimal, it was important to analyze mortality separately in these patients. Accordingly, mortality analyses in MitraClip PSA Cohort patients for whom matches were not obtained (N = 84) within the caliper of 0.25 are reported below.

As noted previously, unmatched MitraClip PSA Cohort patients were slightly older with a higher prevalence of multiple baseline co-morbidities than patients in Matched Cohort 1.

Figure 27 contains Kaplan-Meier curves comparing all-cause mortality in the unmatched MitraClip patients to Matched Cohort 1. Despite the more advanced age and higher prevalence of baseline co-morbidities, mortality at 30 days post-procedure in the unmatched MitraClip patients (4.8%) was comparable to that observed in Matched Cohort 1 (5.5% in MitraClip and 6.5% in Duke). Therefore, procedural mortality in this group of “sicker” patients was no worse than in Matched Cohort 1. At 1 year, mortality in the unmatched MitraClip patients (28.1%) was higher than for Matched Cohort 1 MitraClip patients (21.6%), which is consistent with the observation that this was an older and sicker patient cohort. Importantly, despite being sicker at the baseline, mortality at 12 months in the unmatched MitraClip patients was not worse than that observed in the less sick Matched Cohort 1 Duke patients who were managed non-surgically (28.5% versus 28.1%).

Figure 27: Kaplan-Meier Freedom from All-Cause Mortality, Unmatched MitraClip Patients vs. Matched Cohort 1



One hundred twenty seven (127) patients from the MitraClip PSA Cohort were matched 1-1 to patients in the Duke Cohort. Matches were not obtained for the remaining 84 MitraClip PSA Cohort within a caliper of 0.25. For MitraClip PSA Cohort patients who were matched, there was a 30% relative risk reduction in all-cause mortality at 12 months over the Duke Cohort patients. Since such a mortality comparison could not be performed for the patients who remained unmatched, it is important to compare the improvements in effectiveness measures in the group of MitraClip PSA Cohort who were matched to those who remained unmatched.

The MitraClip device was found to be effective in both matched and unmatched patients. Approximately 83% and 79%, respectively, of surviving matched and unmatched patients experienced freedom from MR > 2+ at 12 months. Reduction in MR severity was accompanied by improvements in Quality of Life, NYHA Functional Class, measures of LV function, and lower rates of CHF hospitalization in both matched and unmatched patients (see Table 101 through Table 107 in Appendix H, Attachment 2).

The magnitude of improvement at 1 year in clinical measures such as LV measurements, NYHA Functional Class, quality of life and heart failure hospitalizations was similar between

the unmatched and matched MitraClip PSA Cohort patients. The improvements in these clinical measures are expected to be associated with better survival outcomes. Therefore, although the baseline hazard (i.e, without treatment with the MitraClip) of 1-year mortality in this “sicker” cohort may be higher than in Matched Cohort 1, it is reasonable to expect that the MitraClip device effect on 1-year mortality would be similar. Thus, had matches been obtained for the 84 unmatched patients, while the corresponding survival curves for the two groups may be expected to be lower than in Matched Cohort 1, the degree of separation between the two groups, MitraClip vs. non-surgical management is expected to be maintained.

H4. CONCLUSIONS

The Duke Cohort was comprised of high surgical risk patients with moderate-to-severe or severe MR who were managed non-surgically. Like the MitraClip PSA Cohort, they had a large number of baseline co-morbidities. However, these patients were significantly younger than patients in the MitraClip PSA Cohort, were more likely to have functional MR, yet had a lower incidence of advanced heart failure symptoms (NYHA Functional Class III/IV) than patients in the MitraClip PSA Cohort. Mortality at 30 days and 1 year in these patients was comparable to estimates in the literature.

In a conservative descriptive analysis, mortality at 30 days post procedure in MitraClip PSA Cohort patients at 5.3% was comparable to the mortality of 6.5% at 30 days in Duke Cohort patients who were managed non-surgically. At 1 year, these rates remained comparable between the two groups, 24.1% in the MitraClip PSA Cohort and 26.2% in the Duke Cohort. These conclusions were unchanged when the Duke Cohort was trimmed (N=527) per the SAP based on age and LVEF to exclude patients who were unlikely to be good matches for MitraClip PSA Cohort patients.

One hundred twenty seven (127) of the 211 patients in the MitraClip PSA Cohort were matched within a caliper of 0.25 to patients in the Trimmed Duke Cohort. After matching, demographic and baseline characteristics were comparable between the two groups, enabling meaningful comparisons of mortality on the basis of therapy received. The point estimate of the 30-day mortality rate was lower in the Cohort 1 MitraClip patients at 5.3% when compared to the rate of 6.3% in the Cohort 1 Duke patients (log rank $p = 0.64$). At 1 year, the hazard ratio of all-cause mortality was 0.70 (95% CI: [0.43, 1.17]) for Cohort 1 MitraClip patients vs. Cohort 1 Duke patients. Therefore, there was a 30% relative risk reduction in all-cause mortality at 1 year due to treatment with the MitraClip. However, this was not statistically significant, likely due to small sample size ($p = 0.172$). LVIDs was the one baseline measure that was statistically significantly different between the two groups in the matched cohort, with a larger average LVIDs in the Cohort 1 MitraClip patients than in the Cohort 1 Duke patients. When the analysis of mortality at 1 year was adjusted for baseline LVIDs, the MitraClip device

effect was slightly larger with a hazard ratio of 0.59 (95% CI: [0.34, 1.00]) for Cohort 1 MitraClip patients vs. Cohort 1 Duke patients. Thus, there was an estimated 41% relative risk reduction in all-cause mortality at 12 months due to treatment with the MitraClip after adjusting for baseline LVIDs. The MitraClip device effect approached statistical significance in this adjusted analysis ($p = 0.049$).

Although matches were not obtained for all 211 MitraClip PSA Cohort patients, results from the mortality comparisons in the matched cohort should be generalizable to the overall cohort of 211 patients for the following reasons: procedural mortality at 30 days in the unmatched MitraClip PSA Cohort patients was no worse than in the Matched Cohort 1 MitraClip patients, improvements in important clinical measures (LV measurements, NYHA Functional Class, quality of life, heart failure hospitalization rates) were similar between unmatched and matched MitraClip patients, and even in a conservative comparison to the matched Duke patients who were less sick at baseline, survival at 1 year in the unmatched MitraClip patients was comparable.

In the subgroup of patients with functional MR from the matched cohort, the estimated MitraClip device effect was consistent with the estimate for the overall matched cohort. Importantly, when the analysis of mortality in FMR patients was adjusted for baseline LVIDs, the MitraClip device effect was larger with a hazard ratio of 0.48, which was statistically significant ($p = 0.017$).

It can therefore be concluded that the MitraClip procedure is safe and does not cause procedural mortality in excess of that observed in matched patients managed non-surgically. The relative risk reduction in all-cause mortality due to treatment with the MitraClip was large at 30%. Thus, in a comparative analysis to a historical matched cohort managed non-surgically at Duke University Medical Center, the benefit-risk profile for the MitraClip was favorable.

Appendix H, Attachment 1

Figure 28: Mountain Plot of Propensity Scores, MitraClip PSA Cohort and Duke Cohort

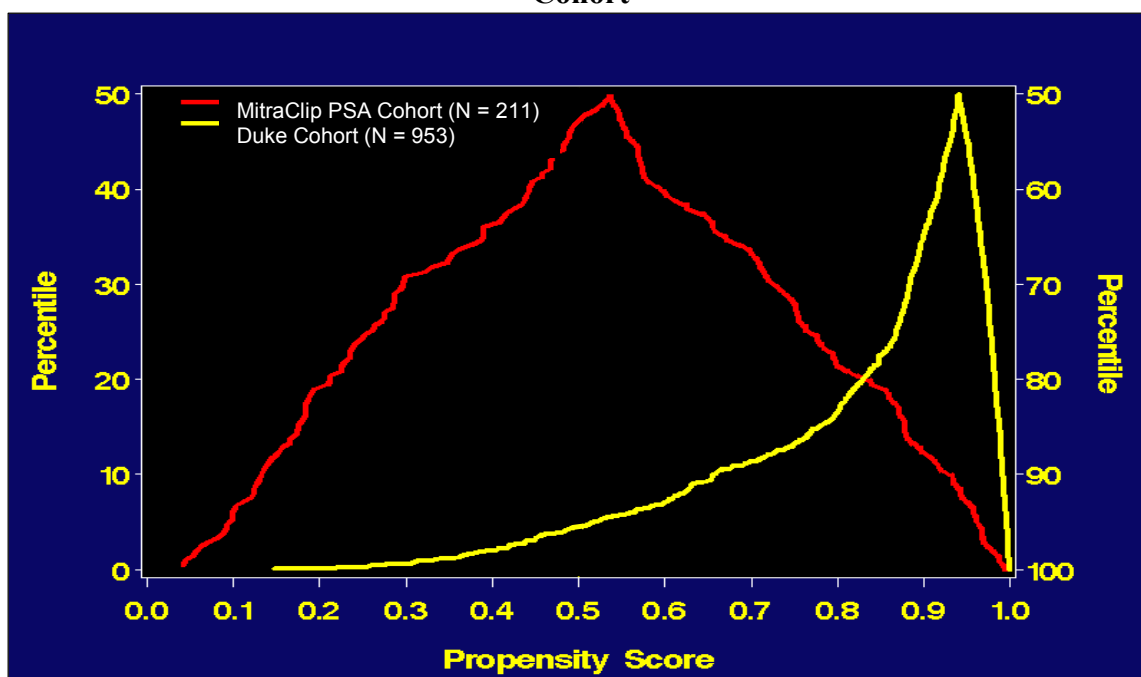
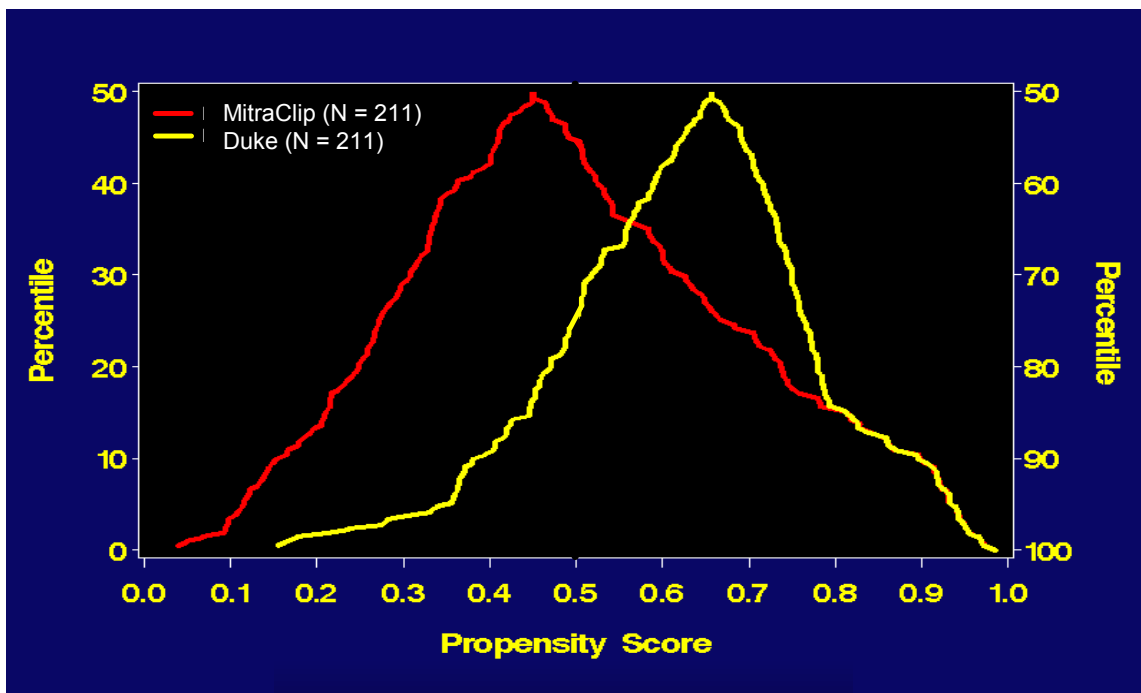


Table 100: Baseline Predictors of Mortality in the Trimmed Duke Cohort (N = 527)

Effect	HR (95% Conf Int)	p-value
Renal Disease	2.17 (1.52, 3.10)	< 0.0001
Diabetes	1.44 (1.03, 2.01)	0.035
NYHA III/IV	1.38 (0.99, 1.92)	0.060
LVEF	0.98 (0.97, 1.002)	0.081

Figure 29: Mountain Plot of Propensity Scores, Matched Cohort 3 (Caliper Size = 0.25, 0.40 or Nearest Propensity Score)



APPENDIX H, Attachment 2

SUBGROUP ANALYSES of MATCHED AND UNMATCHED MITRACLIP PATIENTS TO DUKE PATIENTS

Table 101: Change in SF-36 Quality of Life Score for Matched and Unmatched MitraClip Patients at Baseline and 30 Days

Quality of Life Score	MitraClip Matched Patients (N = 127)		MitraClip Unmatched Patients (N = 84)	
	PCS	MCS	PCS	MCS
N	102	102	62	62
Baseline				
Mean ± SD	33.7 ± 9.9	45.1 ± 13.4	30.8 ± 9.0	44.0 ± 14.0
30 Days				
Mean ± SD	40.0 ± 9.8	48.8 ± 12.5	37.2 ± 9.5	46.4 ± 12.4
Difference				
Mean ± SD	6.3 ± 8.6	3.7 ± 11.5	6.4 ± 10.0	2.5 ± 12.8
p-value (two-sided)	< 0.0001	0.0016	< 0.0001	0.1357

Table 102: Change in SF-36 Quality of Life Score for Matched and Unmatched MitraClip Patients at Baseline and 1 Year

Quality of Life Score	MitraClip Matched Patients (N = 127)		MitraClip Unmatched Patients (N = 84)	
	PCS	MCS	PCS	MCS
N	78	78	40	40
Baseline				
Mean ± SD	34.5 ± 10.1	44.7 ± 13.9	30.5 ± 8.1	42.6 ± 14.0
1 Year				
Mean ± SD	38.1 ± 11.2	51.6 ± 12.9	37.0 ± 11.3	47.7 ± 11.5
Difference				
Mean ± SD	3.6 ± 12.0	6.8 ± 13.0	6.5 ± 9.5	5.1 ± 12.1
p-value (two-sided)	0.0091	< 0.0001	< 0.0001	0.0118

Table 103: NYHA Functional Class for MitraClip Matched and Unmatched Patients at Baseline and Follow-up (Matched Cases)

NYHA Functional Class	Matched Patients (N = 127)		Unmatched Patients (N = 84)	
	Baseline	12 Months	Baseline	12 Months
I	1.1% (1/90)	47.8% (43/90)	0.0% (0/53)	22.6% (12/53)
II	21.1% (19/90)	36.7% (33/90)	3.8% (2/53)	50.9% (27/53)
III	58.9% (53/90)	14.4% (13/90)	64.2% (34/53)	24.5% (13/53)
IV	18.9% (17/90)	1.1% (1/90)	32.1% (17/53)	1.9% (1/53)

Table 104: Left Ventricular Measurements for MitraClip Matched and Unmatched Patients at Baseline and 12 Months (Matched Cases)

	Matched Patients (N = 127)	Unmatched Patients (N = 84)
LVEDV, mL		
N	82	82
Baseline		
Mean ± SD	159.9 ± 53.2	162.1 ± 49.4
12 Months		
Mean ± SD	141.4 ± 49.8	136.2 ± 44.6
Difference		
Mean ± SD	-18.5 ± 33.2	-25.9 ± 26.2
p-value (two-sided)	< 0.0001	< 0.0001
LVESV (cm)		
N	82	49
Baseline		
Mean ± SD	92.8 ± 43.8	69.2 ± 36.6
12 Months		
Mean ± SD	80.9 ± 43.1	65.5 ± 34.4
Difference		
Mean ± SD	-11.9 ± 26.2	-3.6 ± 17.7
p-value (two-sided)	< 0.0001	0.1583

Table 105: Proportion of Patients Free from MR > 2+ for MitraClip Matched and Unmatched Patients

Follow-up	Matched Patients (N = 127)	Unmatched Patients (N = 84)
Baseline	16.4% (20/122)	9.6% (8/83)
Discharge	85.4% (105/123)	83.5% (66/79)
12 Months	83.1% (74/89)	79.2% (42/53)
24 Months	87.5% (14/16)	88.5% (23/26)

Table 106: Proportion of Patients Free from MR > 1+ for MitraClip Matched and Unmatched Patients

Follow-up	Matched Patients (N = 127)	Unmatched Patients (N = 84)
Baseline	0.8% (1/122)	0.0% (0/83)
Discharge	41.5% (51/123)	57.0% (45/79)
12 Months	30.3% (27/89)	39.6% (21/53)
24 Months	18.8% (3/16)	42.3% (11/26)

Table 107: HF Hospitalization for MitraClip Matched and Unmatched Patients

	12 months pre-enrollment	Post-discharge through 12 months	p-value
Matched Patients			
(N = 127)			
% Patients (n/N)	39.4% (50/127)	16.4% (20/122)	< 0.0001
# Events	92	36	
Rate (95% CI)	0.72 (0.59, 0.89)	0.34 (0.25, 0.47)	0.0001
Unmatched Patients			
(N = 84)			
% Patients (n/N)	47.6% (40/84)	16.0% (13/81)	< 0.0001
# Events	74	21	
Rate (95% CI)	0.88 (0.70, 1.11)	0.33 (0.21, 0.50)	< 0.0001

Appendix I EVEREST II Randomized Controlled Trial (RCT)

II. EVEREST II RCT - ELIGIBILITY CRITERIA

Inclusion and exclusion criteria for the EVEREST II RCT are listed below:

Inclusion Criteria

1. Age 18 years or older.
2. Moderate to severe (3+) or severe (4+) chronic mitral valve regurgitation determined as defined in Appendix A and:
3. Symptomatic with $> 25\%$ LVEF and LVESD $\leq 55\text{mm}$ or, asymptomatic with one or more of the following:
 - i. LVEF 25% to 60%
 - ii. LVESD $\geq 40\text{ mm}$
 - iii. New onset of atrial fibrillation
 - iv. Pulmonary hypertension defined as pulmonary artery systolic pressure (PASP) $> 50\text{mmHg}$ at rest or $> 60\text{mmHg}$ with exercise.
4. Candidate for mitral valve repair or replacement surgery, including cardiopulmonary bypass.
5. The primary regurgitant jet originates from malcoaptation of the A2 and P2 scallops of the mitral valve. If a secondary jet exists, it must be considered clinically insignificant.
6. Male or Female. Female subjects of childbearing potential must have a negative pregnancy test within seven (7) days before the procedure.
7. The subject or the subject's legal representative has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board of the respective clinical site.
8. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.
9. Trans-septal catheterization is determined to be feasible by the treating physician.

Exclusion Criteria

1. Evidence of an acute myocardial infarction in the prior 12 weeks of the intended treatment (defined as: Q wave or non-Q wave infarction having CK enzymes $\geq 2X$ the upper laboratory normal limit with the presence of a CK-MB elevated above the institution's upper limit of normal).
2. The need for any other cardiac surgery including surgery for coronary artery disease, atrial fibrillation, pulmonic, aortic or tricuspid valve disease.
3. Any endovascular therapeutic interventional or surgical procedure performed within 30 days prior to the index procedure.
4. In the judgment of the Investigator, the femoral vein cannot accommodate a 24 F catheter or the presence of an inferior vena cava (IVC) filter would interfere with advancement of the catheter or ipsilateral DVT is present.
5. Severe left ventricular dysfunction, defined as an ejection fraction $< 25\%$, and/or end-systolic dimension $> 55\text{mm}$.
6. Mitral valve orifice area $< 4.0\text{ cm}^2$.
7. If leaflet flail is present
 - Flail Width: the width of the flail segment is greater than or equal to 15 mm, or
 - Flail Gap: the flail gap is greater than or equal to 10 mm.
8. If leaflet tethering is present:
 - Coaptation Depth: the mitral valve coaptation depth is more than 11 mm, or
 - Coaptation Length: the vertical coaptation length is less than 2 mm
9. Severe mitral annular calcification.
10. Leaflet anatomy which may preclude clip implantation, proper clip positioning on the leaflets or sufficient reduction in MR. This may include:
 - Evidence of calcification in the grasping area of the A2 and/or P2 scallops
 - Presence of a significant cleft of A2 or P2 scallops
 - More than one anatomic criteria dimensionally near the exclusion limits
 - Bileaflet flail or severe bileaflet prolapse
 - Lack of both primary and secondary chordal support
11. Hemodynamic instability defined as systolic pressure $< 90\text{ mmHg}$ without afterload reduction or cardiogenic shock or the need for inotropic support or intra-aortic balloon pump.
12. Need for emergency surgery for any reason.

-
13. Prior mitral valve surgery or valvuloplasty or any currently implanted mechanical prosthetic valve or currently implanted VAD.
 14. Systolic anterior motion of the mitral valve leaflet.
 15. Hypertrophic cardiomyopathy.
 16. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
 17. History of, or active, endocarditis.
 18. History of, or active, rheumatic heart disease.
 19. History of ASD, whether repaired or not.
 20. History of PFO associated with clinical symptoms (e.g., cerebral ischemia) or previously repaired or when, in the judgment of the investigator, an atrial septal aneurysm is present that may interfere with transseptal crossing.
 21. History of a stroke or documented TIA within the prior 6 months.
 22. Upper GI bleeding within the prior 6 months.
 23. History of bleeding diathesis or coagulopathy or subject will refuse blood transfusions.
 24. Concurrent medical condition with a life expectancy of less than 12 months (see definition in Section 7).
 25. A platelet count $<75,000$ cells/mm³.
 26. Renal insufficiency (Creatinine >2.5 mg/dL).
 27. Active infections requiring current antibiotic therapy (if temporary illness, patients may enroll 2 weeks after discontinuation of antibiotics). Patients must be free from infection prior to treatment. Any required dental work should be completed a minimum of 3 weeks prior to treatment.
 28. Intravenous drug abuse or suspected inability to adhere to follow-up.
 29. Patients in whom transesophageal echocardiography (TEE) is contraindicated.
 30. A known hypersensitivity or contraindication to study or procedure medications which cannot be adequately managed medically.
 31. In the judgment of the Investigator, patients in whom the presence of a permanent pacemaker or pacing leads would interfere with placement of the test device or the placement of the test device would disrupt the leads.
 32. Currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials].
-

12. EVEREST II RCT - STUDY COMPLIANCE

Visit compliance in the EVEREST II RCT was high (>94%) through 3 years (Table 108). Among treated patients (N = 178 in the MitraClip group and N = 80 in the surgical Control group), clinical follow-up occurred in 96.5% of patients at 1 year and in > 85% at 2 years and 3 years.

Table 108: EVEREST II RCT – Study Compliance

Follow-up Visit	# Visits	# Missed Visit	# Deaths before visit	# Withdrawn before visit	Visit Compliance	Clinical Follow-up Occurred In
30-Day	246	8	3	1	96.9%	96.5%
1 Year	225	4	16	13	98.4%	93.4%
2 Years	195	12	25	26	94.8%	85.3%
3 Years	184	7	32	35	96.9%	83.7%

13. EVEREST II RCT – BASELINE DEMOGRAPHIC CHARACTERISTICS AND MEDICAL HISTORY

Baseline characteristics of patients enrolled in the EVEREST II RCT are presented in Table 109.

Table 109: EVEREST II RCT – Baseline Demographic Characteristics and Medical History

Characteristic % (n/N)	MitraClip (N = 184)	Surgical Control (N = 95)	p-value
Age (years), Mean ± SD (N)	67.3±12.8 (184)	65.7±12.9 (95)	0.321
Patients over 75 years of age	29.9% (55/184)	27.4% (26/95)	0.679
Female Gender	37.5% (69/184)	33.7% (32/95)	0.600
Coronary Artery Disease	47.0% (86/183)	46.3% (44/95)	>0.99
Prior Myocardial Infarction	21.9% (40/183)	21.3% (20/94)	>0.99
Atrial Fibrillation History	33.7% (59/175)	39.3% (35/89)	0.415
Prior Stroke	1.6% (3/184)	3.2% (3/95)	0.413
Diabetes	7.6% (14/184)	10.5% (10/95)	0.500
Moderate to Severe Renal Disease	3.3% (6/184)	2.1% (2/95)	0.720
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O ₂)	14.8% (27/183)	14.7% (14/95)	>0.99
Previous Cardiovascular Surgery	22.3% (41/184)	18.9% (18/95)	0.541
Previous Percutaneous Coronary Intervention	24.0% (44/183)	15.8% (15/95)	0.124
NYHA Class III/IV Heart Failure	51.1% (94/184)	47.4% (45/95)	0.614
Functional MR Etiology	26.6% (49/184)	27.4% (26/95)	0.888
LV Ejection Fraction (%), Mean ± SD (N)	60.0±10.1 (182)	60.6±11.0 (95)	0.649
LV Internal Diameter systole (cm), Mean ± SD (N)	3.7±0.9 (181)	3.5±0.8 (94)	0.161

14. EVEREST II RCT – SAFETY RESULTS

Major Adverse Events

Safety of the MitraClip device was measured by the pre-specified primary safety endpoint defined as the proportion of Per Protocol (PP) patients with major adverse events (MAE) at 30 days compared to that of the surgical Control group. MAEs were defined to include significant adverse clinical events associated with the percutaneous and surgical procedures. The PP safety hypothesis is a superiority hypothesis with a 6% delta. Since most patients who did not achieve acute procedural success (APS) underwent standard of care surgery for MR reduction, the PP analysis is biased in favor of the MitraClip group for the safety hypothesis. An unbiased analysis of safety was also conducted with formal hypothesis testing of the safety endpoint on the intention to treat (ITT) cohort, which includes all randomized patients, including MitraClip patients who underwent surgery following the MitraClip procedure and patients who did not undergo treatment (RNT or randomized not treated patients). The ITT safety hypothesis is a superiority hypothesis with a 2% delta. MAEs that occurred as a result of patients that underwent surgery after an unsuccessful MitraClip procedure were included in the ITT MitraClip group.

The primary safety endpoint of MAE rate at 30 days for the PP analysis was met by a wide margin (Table 110). The difference in MAE rate at 30 days between the Device and Control groups for the PP cohort is -47.4% with the upper bound of the 95% confidence limits being -34.4% ($p < 0.0001$) and the difference for the ITT cohort is -32.9% with the upper bound of the 95% confidence limits being -20.7% ($p < 0.0001$). These results surpassed the pre-specified PP and ITT superiority deltas (-6% and -2%, respectively) by a very wide margin. Missing data occurred at a low rate and sensitivity and tipping point analyses showed that these results were robust against missing data.

**Table 110: EVEREST II RCT – Safety Results
CEC Adjudicated Major Adverse Events at 30 Days
Per Protocol and Intention to Treat Cohort**

Analysis Cohort	Safety Superiority	
	Per Protocol (N=217)	Intention to Treat (N=279)
Delta	-6%	-2%
Endpoint Rate (MitraClip)	9.6% (13/136)	15.0% (27/180)
Endpoint Rate (Surgery)	57.0% (45/79)	47.9% (45/94)
Difference	-47.4%	-32.9%
p-value	< 0.0001	< 0.0001
95% CI MitraClip – Surgery	(-60.4%, -34.4%)	(-45.0%, -20.7%)

Per Protocol is defined as patients in MitraClip group who achieved APS and patients in Surgical Control group who underwent surgery.

Intention to Treat is defined as all patients randomized in the trial.

A breakdown of major adverse events is provided in Table 111. The Per Protocol

**Table 111: EVEREST II RCT - Breakdown of Major Adverse Events at 30 Days
Per Protocol and Intention to Treat Cohort**

Description of Event	Per Protocol Cohort (N=217)		Intention to Treat Cohort (N=279)	
	MitraClip % (n/N)	Surgery % (n/N)	MitraClip % (n/N)	Surgery % (n/N)
Death	0.0% (0/136)	2.5% (2/79)	1.1% (2/180)	2.1% (2/94)
Myocardial infarction	0.0% (0/136)	0.0% (0/79)	0.0% (0/180)	0.0% (0/94)
Re-operation for failed surgical repair or replacement	0.0% (0/136)	1.3% (1/79)	0.0% (0/180)	1.1% (1/94)
Non-elective cardiovascular surgery for adverse events	0.0% (0/136)	5.1% (4/79)	2.2% (4/180)	4.3% (4/94)
Stroke	0.0% (0/136)	2.5% (2/79)	1.1% (2/180)	2.1% (2/94)
Renal Failure	0.0% (0/136)	0.0% (0/79)	0.6% (1/180)	0.0% (0/94)
Deep wound infection	0.0% (0/136)	0.0% (0/79)	0.0% (0/180)	0.0% (0/94)
Ventilation > 48 hours	0.0% (0/136)	5.1% (4/79)	0.0% (0/180)	4.3% (4/94)
GI complication requiring surgery	0.7% (1/136)	0.0% (0/79)	1.1% (2/180)	0.0% (0/94)
New onset of permanent AF	0.0% (0/136)	0.0% (0/79)	1.1% (2/180)	0% (0/94)
Septicemia	0.0% (0/136)	0.0% (0/79)	0.0% (0/180)	0.0% (0/94)
Transfusion of ≥ 2 units of blood	8.8% (12/136)	53.2% (42/79)	13.3% (24/180)	44.7% (42/94)
Total^c	9.6% (13/136)	57.0% (45/79)	15.0% (27/180)	47.9% (45/94)

^a Total number of patients may not equal the sum of patients in each row since one patient may experience multiple events.

While the MitraClip group was superior in the primary safety endpoint, a significant component of the safety advantage in MAE rates was the lower rate of transfusions (some of which were for prophylaxis) at 30 days. A sensitivity analysis was carried out where transfusions were replaced by major bleeding complications defined as procedure-related bleeding requiring transfusions ≥ 2 units or surgery. The Per Protocol and Intention to Treat safety hypotheses were met with these analyses.

**Table 112: EVEREST II RCT – Sensitivity Analysis of Safety Endpoints
CEC Adjudicated Major Adverse Events at 30 Days (Major Bleeding Complication)
Per Protocol and Intention to Treat Cohort**

Analysis Cohort	Safety Superiority	
	Per Protocol (N=217)	Intention to Treat (N=279)
Delta	-6%	-2%
Endpoint Rate (MitraClip)	4.4% (6/136)	8.3% (15/180)
Endpoint Rate (Surgery)	50.6% (40/79)	42.6% (40/94)
Difference	-46.2%	-34.2%
p-value	< 0.0001	< 0.0001
95% CI MitraClip – Surgery	(-58.8%, -33.7%)	(-45.8%, -22.6%)

Per Protocol is defined as patients in MitraClip group who achieved APS and patients in Surgical Control group who underwent surgery.

Intention to Treat is defined as all patients randomized in the trial.

All secondary safety endpoints at 30 days trended in favor of the MitraClip group over surgical Control, with the exception of major vascular complications associated with the percutaneous procedure (4.9% MitraClip, 0% Surgery).

**Table 113: EVEREST II RCT - CEC Adjudicated Other Secondary Safety Endpoints
at 30 Days**

Description of Event	Intention to Treat Cohort (N = 279)	
	MitraClip % (n/N)	Surgery % (n/N)
Major Vascular Complication	4.9% (9/184)	0.0% (0/95)
Major Bleeding Complication	4.9% (9/184)	40.0%(38/95)
Non-Cerebral Thromboembolism	0.5% (1/184)	2.1% (2/95)
Dysrhythmia	4.9% (9/184)	23.2% (22/95)
Endocarditis	0.5% (1/184)	1.1% (1/95)
Thrombosis	0.0% (0/184)	0.0% (0/95)
Hemolysis	0.0% (0/184)	0.0% (0/95)
Clinically Significant Atrial Septal Defect (Treated)	1.1% (2/184)	0.0% (0/95)

15. EVEREST II RCT – EFFECTIVENESS RESULTS

The primary effectiveness endpoint of Clinical Success (freedom from death, mitral valve surgery or re-operation, and MR > 2+ at 1 year) is summarized in Table 114. These analyses were repeated, as requested by FDA, with Clinical Success defined as freedom from death, mitral valve surgery or re-operation, and MR > 1+ at 1 year (Table 115).

Table 114: EVEREST II RCT - Summary of Effectiveness Results
Freedom from death, mitral valve surgery/re-operation, and MR > 2+ at 1 Year
Per Protocol and Intention to Treat Cohort

Analysis Cohort	Effectiveness (margin of reduced effectiveness)	
	Per Protocol (N=217)	Intention to Treat (N=279)
Delta	-31%	-25%
Endpoint Rate (MitraClip)	72.4% (97/134)	67.4% (118/175)
Endpoint Rate (Surgery)	87.8% (65/74)	73.0% (65/89)
Difference	-15.4%	-5.6%
p-value	0.0012	0.0002
95% LCB MitraClip - Surgery	-25.4%	-16.1%

Table 115: EVEREST II RCT – Re-Analysis of Effectiveness Endpoint
Freedom from death, mitral valve surgery/re-operation, and MR > 1+ at 1 Year
Per Protocol and Intention to Treat Cohort

Analysis Cohort	Effectiveness (margin of reduced effectiveness)	
	Per Protocol (N=163)	Intention to Treat (N=279)
Delta	-31%	-25%
Endpoint Rate (MitraClip)	45.1% (37/82)	33.7% (59/175)
Endpoint Rate (Surgery)	68.9% (51/74)	57.3% (51/89)
Difference	-23.8%	-23.6%
p-value	0.1692	0.4117
95% LCB MitraClip - Surgery	-37.7%	-34.9%%

Components of failure of the Clinical Success endpoint are provided in Table 116 (Per Protocol) and Table 117 (Intention to Treat).

**Table 116: Components of Failure of Clinical Success at 1 Year
Per Protocol Cohort (N = 217)**

Component of Failure	MitraClip % (n/N)	Surgery % (n/N)	MitraClip-Surgery (95% Two-sided Conf Int)
Death	4.5% (6/134)	6.8% (5/74)	-2.3% (-10.0%, 5.5%)
MV surgery (MitraClip group) or Re-operation (Surgery group)	6.7% (9/134)	2.7% (2/74)	4.0% (-2.7%, 10.7%)
MR > 2+ at 1 year	16.4% (22/134)	2.7% (2/74)	13.7% (5.4%, 22.0%)
Total	27.6% (37/134)	12.2% (9/74)	15.4% (3.8%, 27.1%)

**Table 117: Components of Failure of Clinical Success at 1 Year
Intention to Treat Cohort (N = 279)**

Component of Failure	MitraClip % (n/N)	Surgery % (n/N)	MitraClip-Surgery (95% Two-sided Conf Int)
Death	6.3% (11/175)	5.6% (5/89)	0.7% (-6.2%, 7.5%)
MV surgery (MitraClip group) or Re-operation (Surgery group)	5.1% (9/175)	2.2% (2/89)	2.9% (-2.4%, 8.2%)
MR > 2+ at 1 year	21.1% (37/175)	19.1% (17/89)	2.0% (-9.0%, 13.1%)
Total	32.6% (57/175)	27.0% (24/89)	5.6% (-6.8%, 18.0%)

Components of failure of freedom from death, mitral valve surgery or re-operation, and MR > 1+ at 1 year are provided in Table 118 and Table 119.

Table 118: Components of Failure of Clinical Success (1+ MR definition) at 1 Year Per Protocol Cohort 1+ (N = 163)

Component of Failure	MitraClip % (n/N)	Surgery % (n/N)	MitraClip-Surgery (95% Two-sided Conf Int)
Death	3.7% (3/82)	6.8% (5/74)	-3.1% (-11.4%, 5.2%)
MV surgery (MitraClip group) or Re-operation (Surgery group)	3.7% (3/82)	2.7% (2/74)	1.0% (-5.8%, 7.7%)
MR > 1+ at 1 year	47.6% (39/82)	21.6% (16/74)	25.9% (10.3%, 41.5%)
Total	54.9% (45/82)	31.1% (23/74)	23.8% (7.4%, 40.2%)

Table 119: Components of Failure of Clinical Success (1+ MR definition) at 1 Year Intention to Treat Cohort (N = 279)

Component of Failure	MitraClip % (n/N)	Surgery % (n/N)	MitraClip-Surgery (95% Two-sided Conf Int)
Death	6.3% (11/175)	5.6% (5/89)	0.7% (-6.2%, 7.5%)
MV surgery (MitraClip group) or Re-operation (Surgery group)	5.1% (9/175)	2.2% (2/89)	2.9% (-2.4%, 8.2%)
MR > 1+ at 1 year	54.9% (96/175)	34.8% (31/89)	20.0% (6.8%, 33.2%)
Total	66.3% (116/175)	42.7% (38/89)	23.6% (10.3%, 36.9%)

Robustness of analyses of the primary effectiveness endpoint (freedom from death, surgery or re-operation, and MR > 2+) for the PP and ITT analyses are evaluated by carrying out various sensitivity analyses, including multiple imputations and worst case analyses. All sensitivity analyses show that the endpoint was met.

Change in left ventricular volumes and dimensions from baseline to 1 year are summarized in Table 120. Sequential hypotheses testing of measures of left ventricular function demonstrated statistically significant reductions from baseline to 1 year in LVEDV, LVIDd, and LVESV, and a trend toward a reduction in LVIDs, for both groups. As surgery results in a greater degree of MR reduction, there was a greater reduction in left ventricular size in the surgical Control group.

Table 120: EVEREST II RCT Change in LV Measurement from Baseline to 1 Year Per Protocol Cohort (N = 217)
Surviving Patients with Paired Data at Baseline and 1 Year

LV Measurement	MitraClip (N = 137)	Surgery (N = 80)	Two-sided p-value (between-group)
Change in LVEDV, ml			
Mean ± SD (N)	-21.3±24.1 (118)	-40.2±36.2 (65)	<0.001
One-sided p-value (within-group)	<0.001	<0.001	
Change in LVIDd, cm			
Mean ± SD (N)	-0.4±0.5 (122)	-0.6±0.6 (66)	0.003
One-sided p-value (within-group)	<0.001	<0.001	
Change in LVESV, ml			
Mean ± SD (N)	-4.4±14.0 (118)	-5.1±20.8 (65)	0.789
One-sided p-value (within-group)	0.001	0.026	
Change in LVIDs, cm			
Mean ± SD (N)	-0.1±0.5 (120)	-0.0±0.6 (66)	0.407
One-sided p-value (within-group)	0.056	0.479	

The improvement in LV function for both MitraClip and surgical Control groups resulted in improvements in NYHA Functional Class and SF-36 quality of life (Table 121). NYHA Functional Class III or IV symptoms decreased from 50.0% of patients at baseline to only 2.4% of patients at 1 year in the MitraClip group and from 45.5% to 12.1% in the surgical Control group. Both the physical component summary (PCS) and mental component summary (MCS) SF-36 quality of life (QOL) scores increased over baseline levels at 1 year in both groups. Both groups experienced improvement in PCS that was larger than the minimal clinically important difference (3.1). Both groups experienced an improvement in MCS of at least MCID the minimal clinically important difference (3.8).

Improvements in NYHA Class and quality of life are consistent with a clinically meaningful reduction in MR accompanied by reverse left ventricular remodeling.

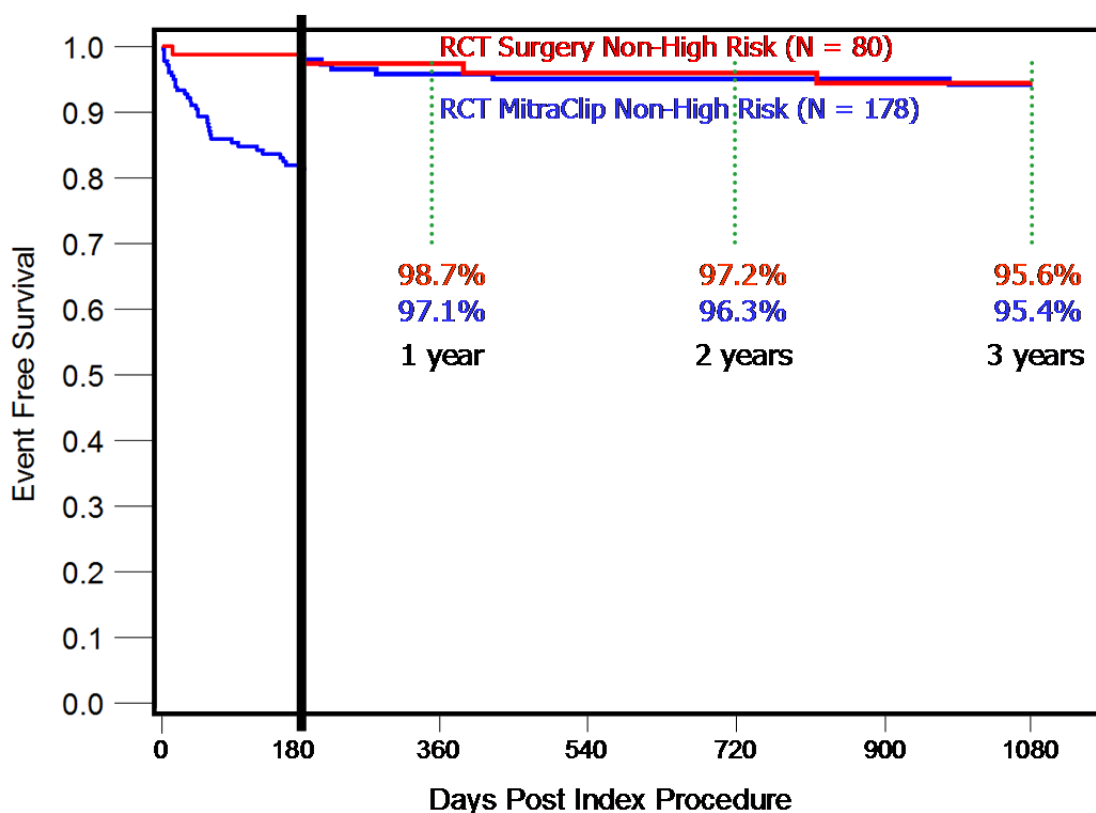
Table 121: EVEREST II RCT Summary of NYHA Functional Class and SF-36 QOL Per Protocol Cohort (N = 217)
Surviving Patients with Paired Data at Baseline and 1 Year

Endpoint	MitraClip (N = 137)		Surgery (N = 80)	
	Baseline	1 Year	Baseline	1 Year
NYHA Functional Class III/IV, % (n/N)	50.0% (62/124)	2.4% (3/124)	45.5% (30/66)	12.1% (8/66)
Quality of Life, Physical Component Summary Score				
Mean ± SD (N)	41.7±9.7 (110)	46.3±9.1 (110)	42.5±11.1 (60)	47.0±10.4 (60)
Quality of Life, Mental Component Summary Score				
Mean ± SD (N)	47.5±11.3 (111)	53.3±7.5 (111)	47.0±11.6 (60)	50.8±9.8 (60)

16. EVEREST II RCT – DURABILITY RESULTS

In patients treated with the MitraClip, mitral valve surgery occurred in approximately 20% of patients through 6 months. Beyond 6 months, mitral valve surgery occurred at a low rate in the MitraClip group (see Figure 30 for landmark analysis for freedom from mitral valve surgery).

**Figure 30: EVEREST II RCT - Kaplan-Meier Freedom from Mitral Valve Surgery or Re-operation – 6-Month Landmark Analysis
All Treated Patients (N = 258)**



At 1 year, 2 years and 3 years, freedom from mitral valve surgery in the MitraClip group were 78.9%, 78.2% and 77.6% respectively and freedom from re-operation in the surgical Control group were 97.4%, 96.0% and 94.4% respectively. Analyses of durability show that beyond 1 year the Device and Control groups deteriorate at the same rate, and there is no evidence of acceleration of deterioration in the Device group over the Control group. In fact, differences between the Device and Control groups reduce or remain stable from 1 year to 3 years consistently for all three outcomes.

Table 122: EVEREST II RCT Durability, All Treated Patients (N = 258)

	MitraClip (N = 178)	Surgery (N = 80)	Difference (MitraClip - Surgery)
Freedom from MR > 2+ in surviving patients			
1 year	81.2%	98.5%	-17.3%
2 years	85.0%	96.5%	-11.5%
3 years	84.2%	96.0%	-11.8%
Freedom from MR > 1+ in surviving patients			
1 year	42.9%	77.3%	-34.4%
2 years	36.2%	84.2%	-48.0%
3 years	40.0%	86.0%	-46.0%
Freedom from Mitral Valve Surgery/Re-operation			
1 year	78.9%	97.4%	-18.5%
2 years	78.2%	96.0%	-17.8%
3 years	77.6%	94.4%	-16.8%
Freedom from Death and Mitral Valve Surgery/Re-operation			
1 year	74.6%	91.1%	-16.5%
2 years	71.0%	87.0%	-16.0%
3 years	68.0%	81.4%	-13.4%
Freedom from Death, Mitral Valve Surgery/Re-operation and MR > 2+			
1 year	61.8%	89.0%	-27.2%
2 years	56.8%	82.8%	-26.0%
3 years	53.8%	77.9%	-24.1%
Freedom from Death, Mitral Valve Surgery/Re-operation and MR > 1+			
1 year	30.5%	76.5%	-46.0%
2 years	25.8%	70.7%	-44.9%
3 years	23.2%	66.8%	-43.6%

Table 123 and Table 124 show durability of reduction in left ventricular volumes and freedom from NYHA Class III or IV in the MitraClip and Surgery groups in the Per Protocol cohort. The table shows sustained reduction in left ventricular volumes and improvements in NYHA Class.

**Table 123: EVEREST II RCT – Durability of Reduction in Left Ventricular Volumes
Per Protocol Cohort**

LV Measurement		Difference (Follow-up – Baseline)	
		MitraClip	Surgery
LVEDV, ml			
Mean ± SD (N)	1-Year	-21.3 ± 24.1 (118)	-40.2 ± 36.2 (65)
	2-Year	-31.3 ± 25.2 (107)	-48.5 ± 35.9 (56)
	3-Year	-25.5 ± 25.3 (98)	-44.3 ± 28.8 (47)
LVESV, ml			
Mean ± SD (N)	1-Year	-4.4 ± 14.0 (118)	-5.1 ± 20.8 (65)
	2-Year	-7.3 ± 17.0 (107)	-9.1 ± 17.0 (56)
	3-Year	-5.2 ± 16.2 (98)	-11.5 ± 12.7 (47)

**Table 124: EVEREST II RCT – Durability of Improvement in NYHA Class
Per Protocol Cohort**

Surviving Patients with Paired Data at Baseline and Follow-up		Proportion of Patients	
		MitraClip	Surgery
Freedom from NYHA Class III or IV	Baseline → 1-Year (N)	50.0% → 97.6% (124)	54.6% → 87.9% (66)
	Baseline → 2-Year (N)	53.6% → 99.1% (112)	51.7% → 90.0% (60)
	Baseline → 3-Year (N)	55.3% → 96.1% (103)	60.0% → 98.0% (50)

Appendix J ACCESS-EU Findings (European Post-Market Study)

The MitraClip System received CE Mark in March 2008, and is indicated in European Union for reconstruction of the insufficient mitral valve through tissue approximation. ACCESS-EU is an ongoing prospective, single-arm, multicenter post-approval observational study of MitraClip for the treatment of mitral regurgitation (MR) in Europe. The primary objective of the ACCESS-EU study is to gain information with respect to health economics and clinical care, and to provide further evidence of safety and effectiveness. Phase I of the study has completed enrollment of 567 patients, with 487 patients having completed 1-year follow-up. Phase II of ACCESS-EU, with the objective of collecting additional clinical data, specifically Echocardiography Core Laboratory evaluation of MR severity and other echocardiographic measures, is actively enrolling with over 280 patients enrolled as of January 2013 and follow-up ongoing.

Patients in ACCESS-EU had a mean age of 73.7 years, 63.8% male, and a history of CHF (70.1%), coronary artery disease (62.7%), atrial fibrillation (67.7%) and hypertension (76.1%). 84.9% were NYHA III/IV, and the mean LVEF was 35%. Cardiac operative risk was evaluated using the EuroScore, a method more commonly used outside the US for assessing risk. The mean logistic EuroScore was 23.0% and 44.6% of patients had a logistic EuroScore of 20% or greater.

The results of ACCESS-EU Phase I at 1 year represent a population with significant, symptomatic MR, a high rate of multiple serious comorbidities, and high surgical risk. 30 day mortality and 1 year mortality were 3.4% and 17.3%, respectively. Stroke, myocardial infarction and cardiac tamponade all occurred at less than 1.5% at 1 year. Considering the high MitraClip device implant rate (99.6%, 565/567), the high rate of meaningful MR reduction (78.9%, 258/327 MR<2+), and the resulting improvements in 6-minute walk (59.5m difference, $p<0.0001$), quality of life score (13.5 point improvement, $p<0.0001$) and NYHA Functional Class (71.5% NYHA Class I or II, $p<0.0001$), at 1 year, it is concluded that the MitraClip device provides an important therapeutic option for patients with significant mitral regurgitation, and is especially important for patients who may be considered high surgical risk. The ACCESS-EU Phase I Study results support a positive benefit/risk profile for the MitraClip Device.

Table 125: Patient Characteristics in the ACCESS-EU Study

Characteristic ^a	ACCESS-EU Phase I (N=567)
Age, years	
Mean±SD (N)	73.7 ±9.6 (567)
Patients over 75 years of age	45.1% (256/567)
Male Gender	63.8% (362/567)
Body Mass Index, kg/m ² Mean±SD (N)	25.9 ±4.4 (535)
Congestive Heart Failure	70.1% (397/566)
Coronary Artery Disease	62.7% (354/565)
Myocardial infarction	32.0% (175/547)
Atrial fibrillation	67.7% (356/526)
Cerebrovascular disease	12.9% (73/566)
Cardiomyopathy	46.2% (259/561)
Hypertension	76.1% (429/564)
Diabetes	29.6% (168/567)
Moderate to Severe Renal Disease	41.6% (236/567)
Previous Cardiovascular Surgery	
Coronary artery bypass graft	28.9% (164/567)
Aortic valve surgery	8.8% (50/567)
Tricuspid valve surgery	0.5% (3/567)
Previous PCI, % (n/N)	38.2% (213/558)
Cardiac Rhythm Device Implant	
Pacemaker	12.7% (70/552)
ICD	16.7% (92/552)
NYHA Functional Class	
I	1.3% (7/549)
II	13.8% (76/549)
III	69.9% (384/549)
IV	14.9% (82/549)
LV Ejection Fraction, %	
Median (N)	35% (561)
LV Internal Diameter, systole, cm	
Mean±SD (N)	4.6 ±1.5 (322)
Logistic EuroScore	
(Mean ± SD (N))	23.0±18.3 (567)
Logistic EuroScore ≥ 20%	44.6% (253/567)

^a Sample sizes or denominators smaller than 567 reflect missing data.

Table 126: Safety Outcomes at 30 days and 1 Year in ACCESS-EU

Adverse Event Description	30 Days	1 Year
Death	3.4% (19/567)	17.3% (98/567)
Stroke	0.7% (4/567)	1.1% (6/567)
Myocardial Infarction	0.7% (4/567)	1.4% (8/567)
Respiratory Failure	0.7% (4/567)	0
Need for Resuscitation	1.8% (10/567)	0
Cardiac Tamponade	1.1% (6/567)	1.2% (7/567)

Table 127: Number of MitraClip Devices Implanted

Number of Clips Implanted	ACCESS-EU
0	0.4% (2/567)
1	60.1% (341/567)
2	36.7% (208/567)
3	2.6% (15/567)
4	0.2% (1/567)

Table 128: ACCESS-EU MR Severity at Baseline and 1 Year, Paired Data

MR Severity	Baseline	1 Year	p-value
0: None	0.0% (0/327)	2.8% (9/327)	< 0.0001
1+: Mild	0.0% (0/327)	27.8% (91/327)	
2+: Moderate	3.1% (10/327)	48.3% (158/327)	
3+: Moderate-to-Severe	45.0% (147/327)	16.5% (54/327)	
4+: Severe	52.0% (170/327)	4.6% (15/327)	

Table 129: ACCESS-EU NYHA Baseline to 1 Year, Paired Data

NYHA Functional Class	Baseline	1 Year	p-value
I	1.7% (6/343)	25.1% (86/343)	< 0.0001
II	16.0% (55/343)	46.4% (159/343)	
III	72.3% (248/343)	26.8% (92/343)	
IV	9.9% (34/343)	1.7% (6/343)	

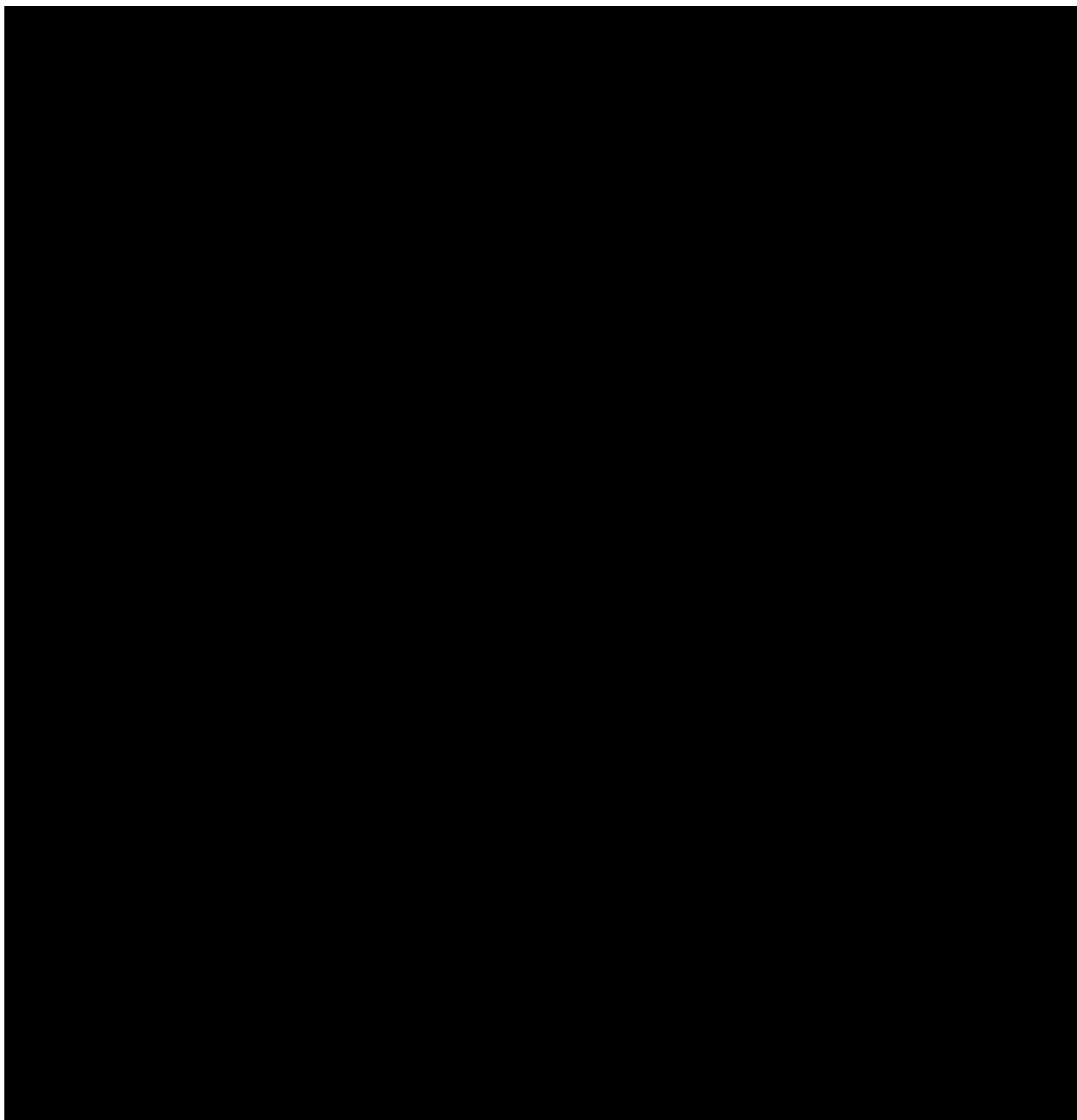
Table 130: ACCESS-EU 6 Minute Walk, Paired Data

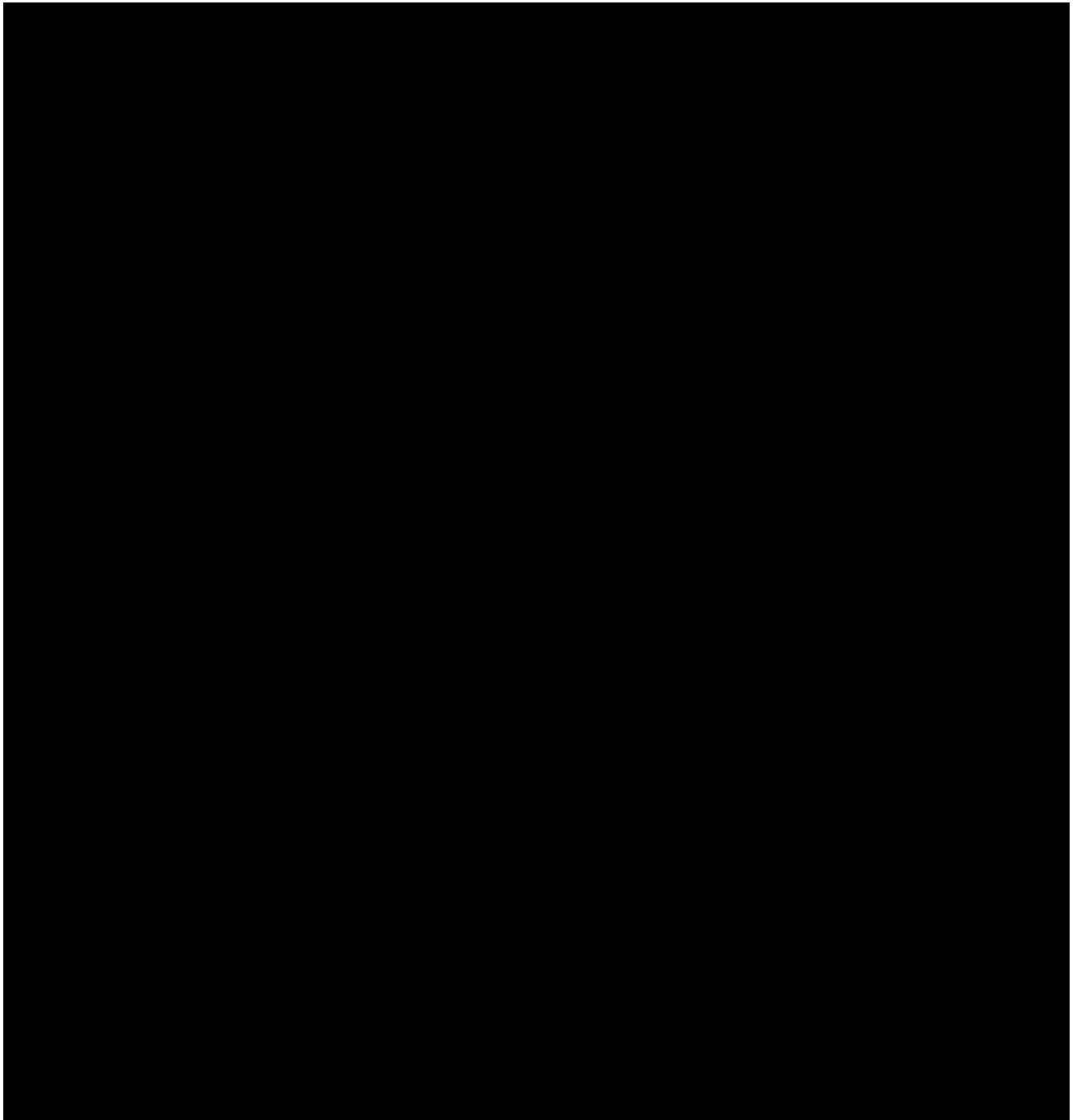
6-Minute Walk Distance (meters)	N	Baseline	1 Year	Difference (1 Year - Baseline)	95% Two-sided Conf Int p-value
Mean ± SD	216	274.7±118.7	334.2 ±127.9	59.5±112.4	(44.5, 74.6) < 0.0001
Median		280.5	344.0	60.5	

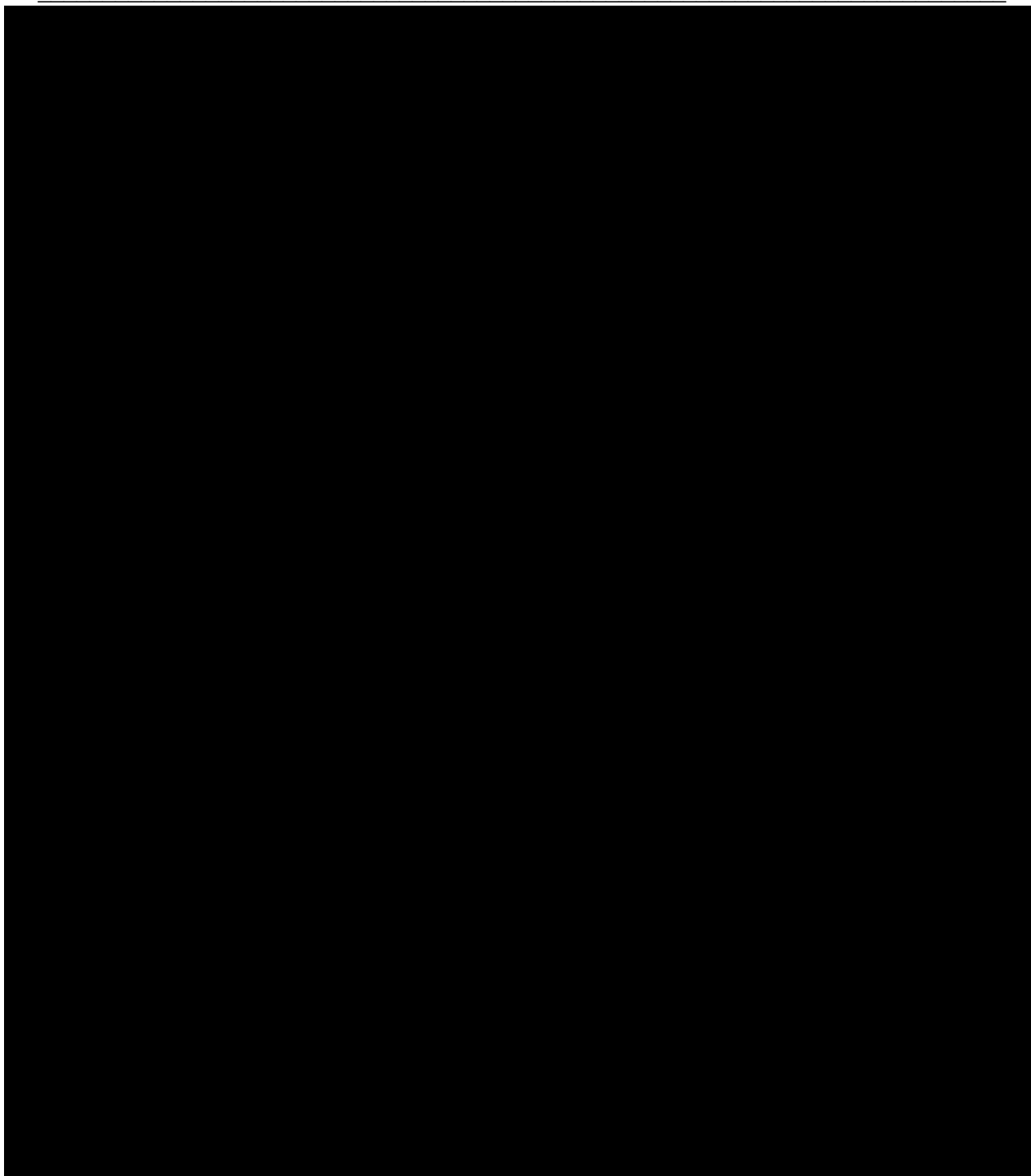
Table 131: ACCESS-EU Quality of Life Score

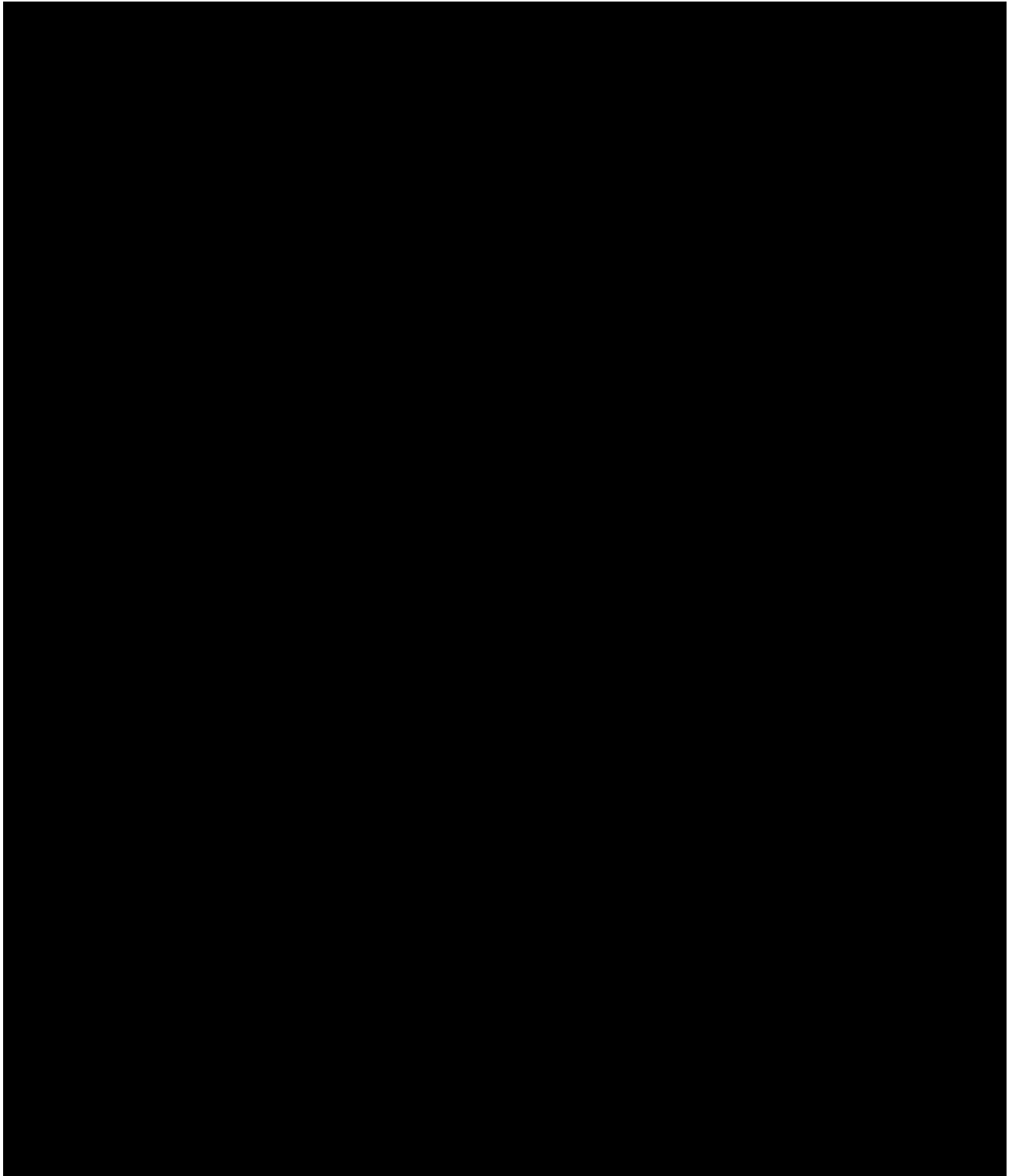
Quality of Life Score	N	Baseline	1 Year	Difference (1 Year - Baseline)	95% Two-sided CI p-value
Mean ± SD	264	41.6±18.9	28.1±20.1	-13.5±20.5	(-16.0, -11.0) < 0.0001
Median		41.5	23.5	-14.0	

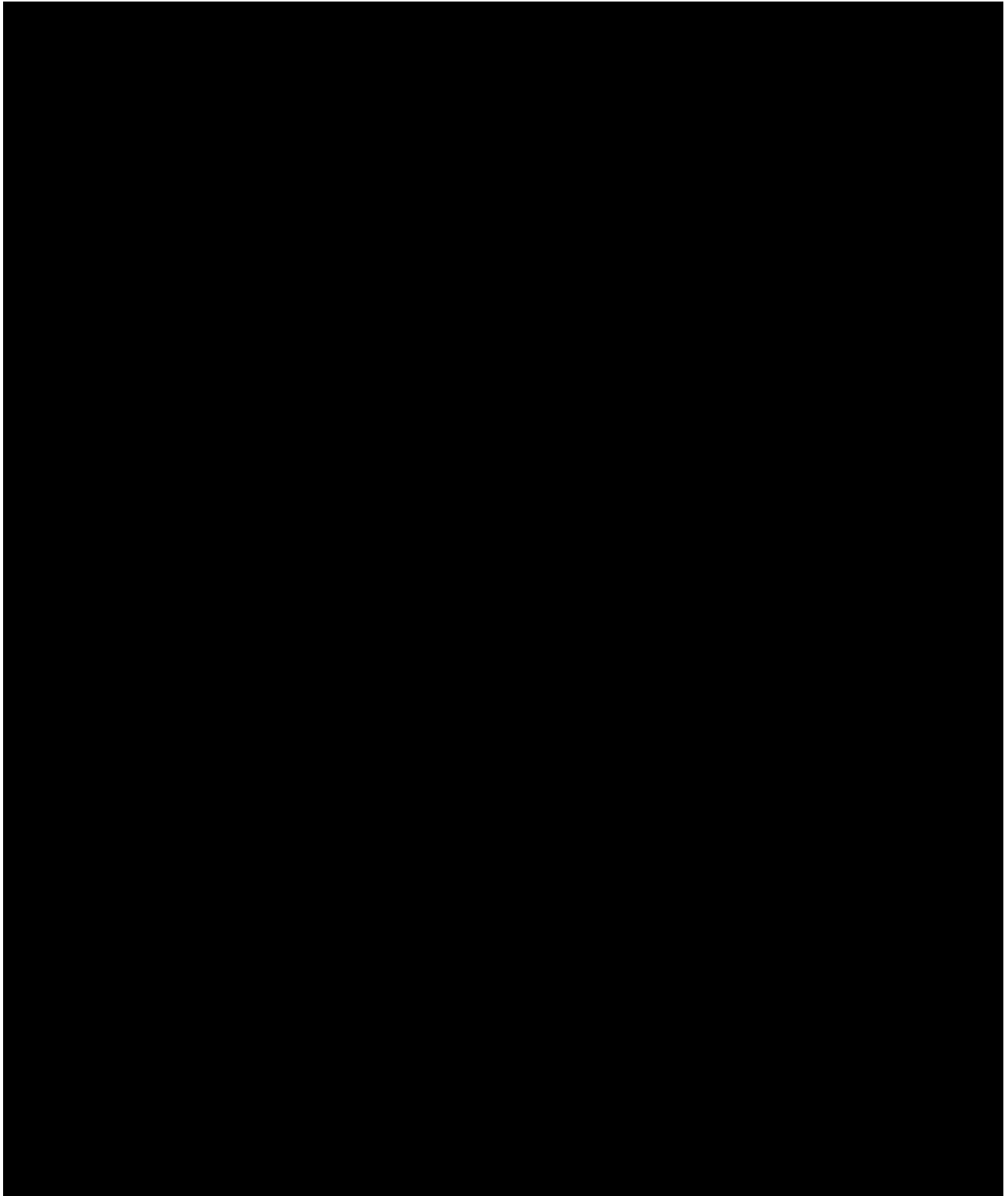
Appendix K Death Narratives (30-Day)

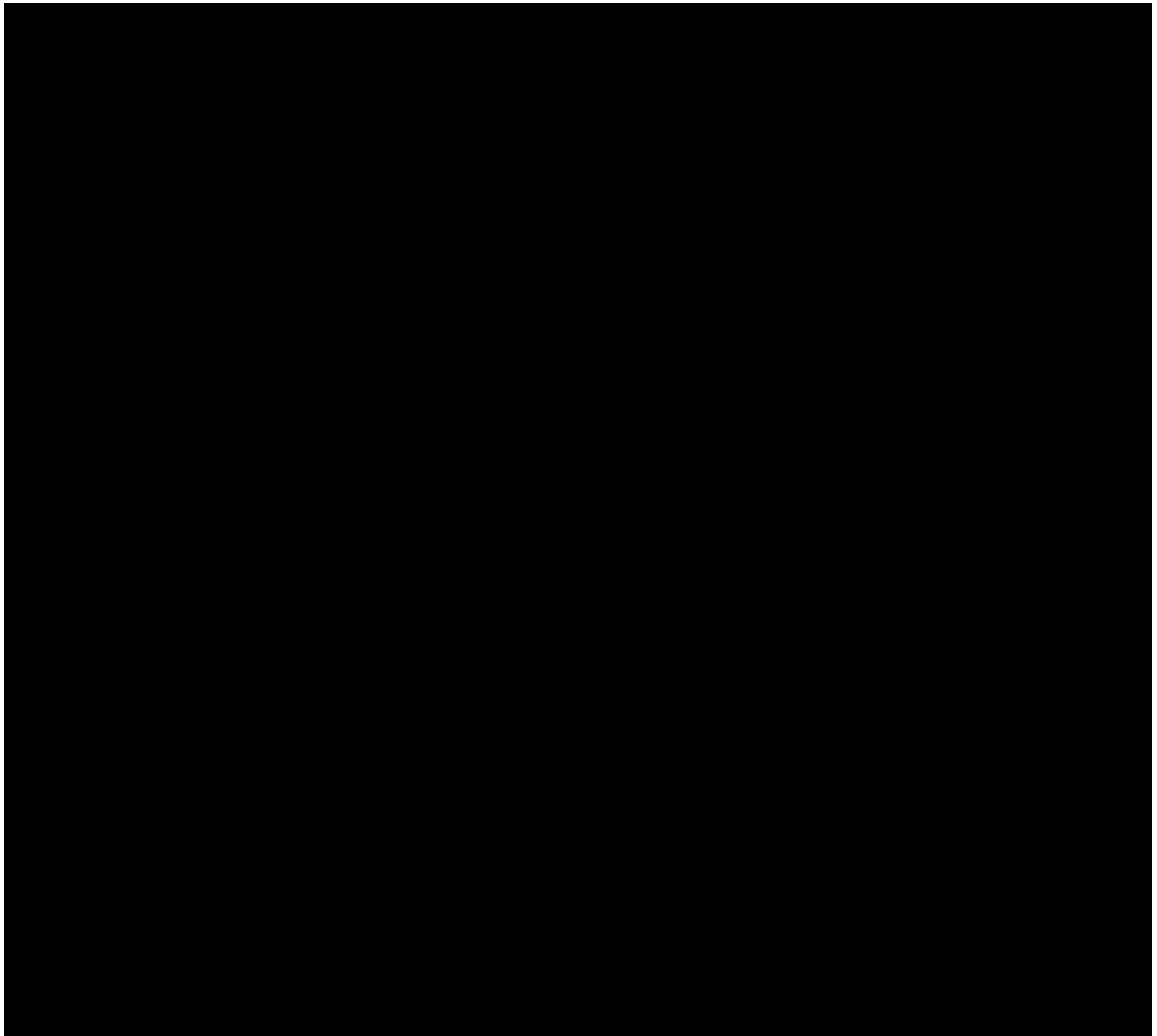


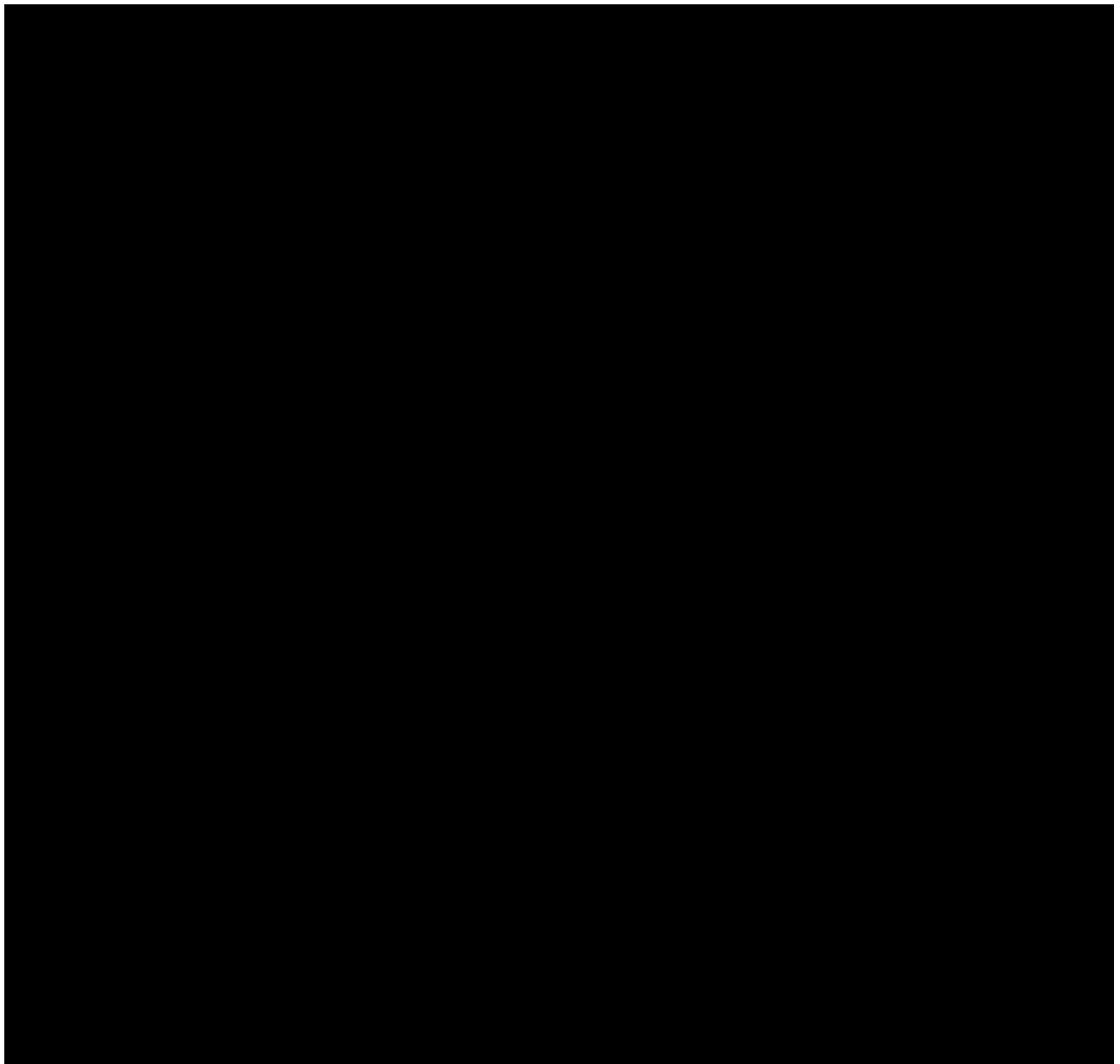


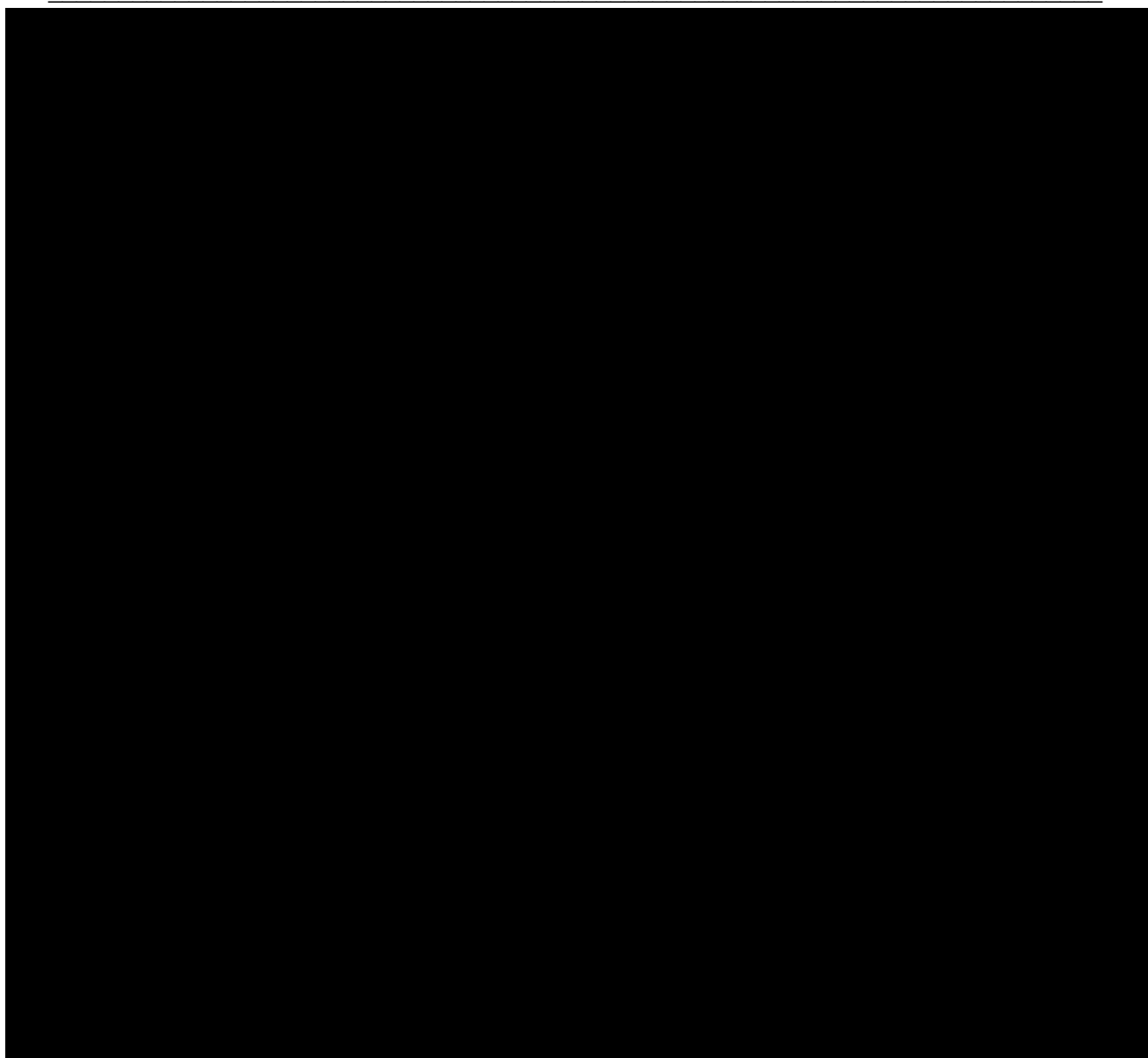


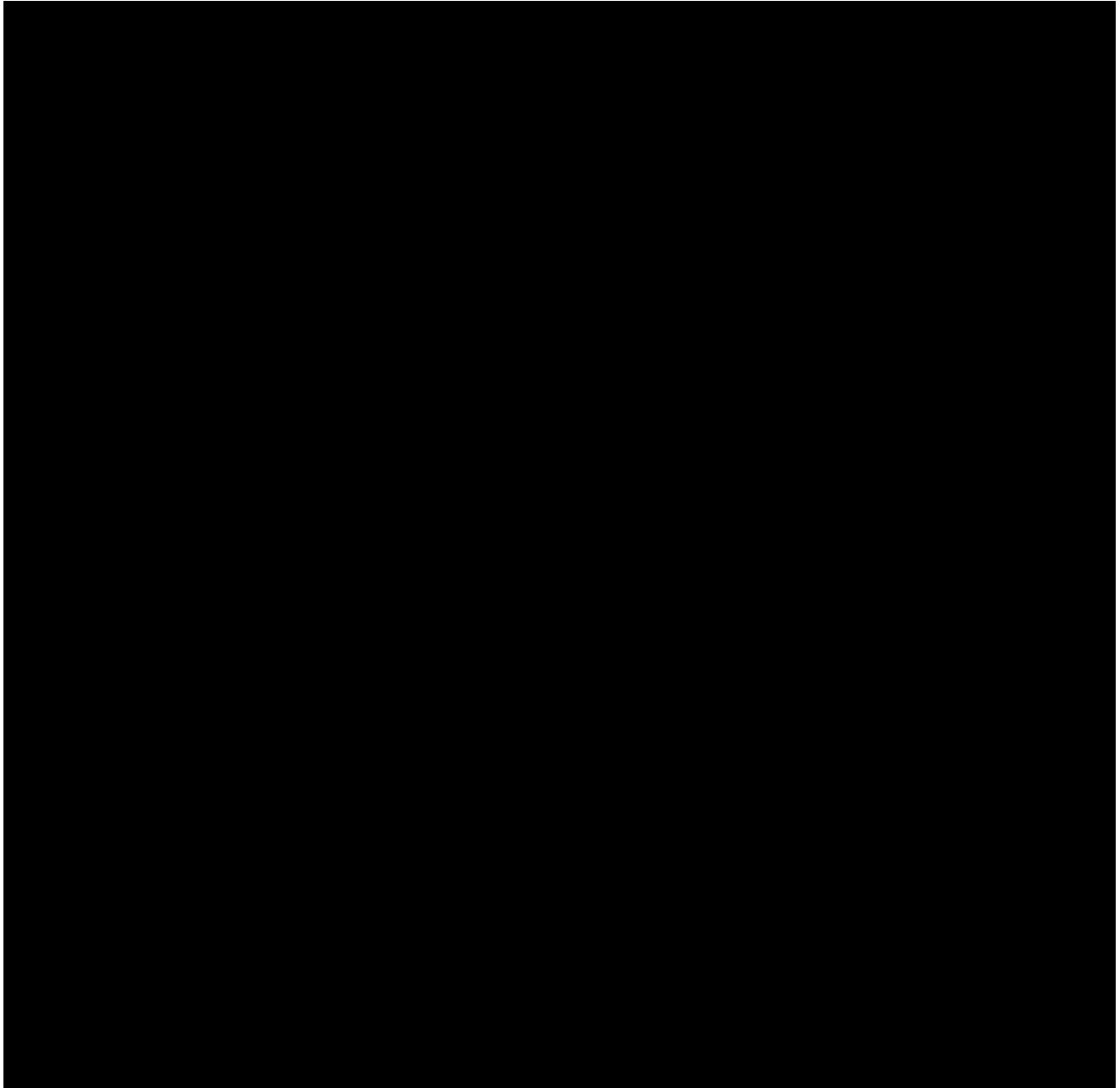


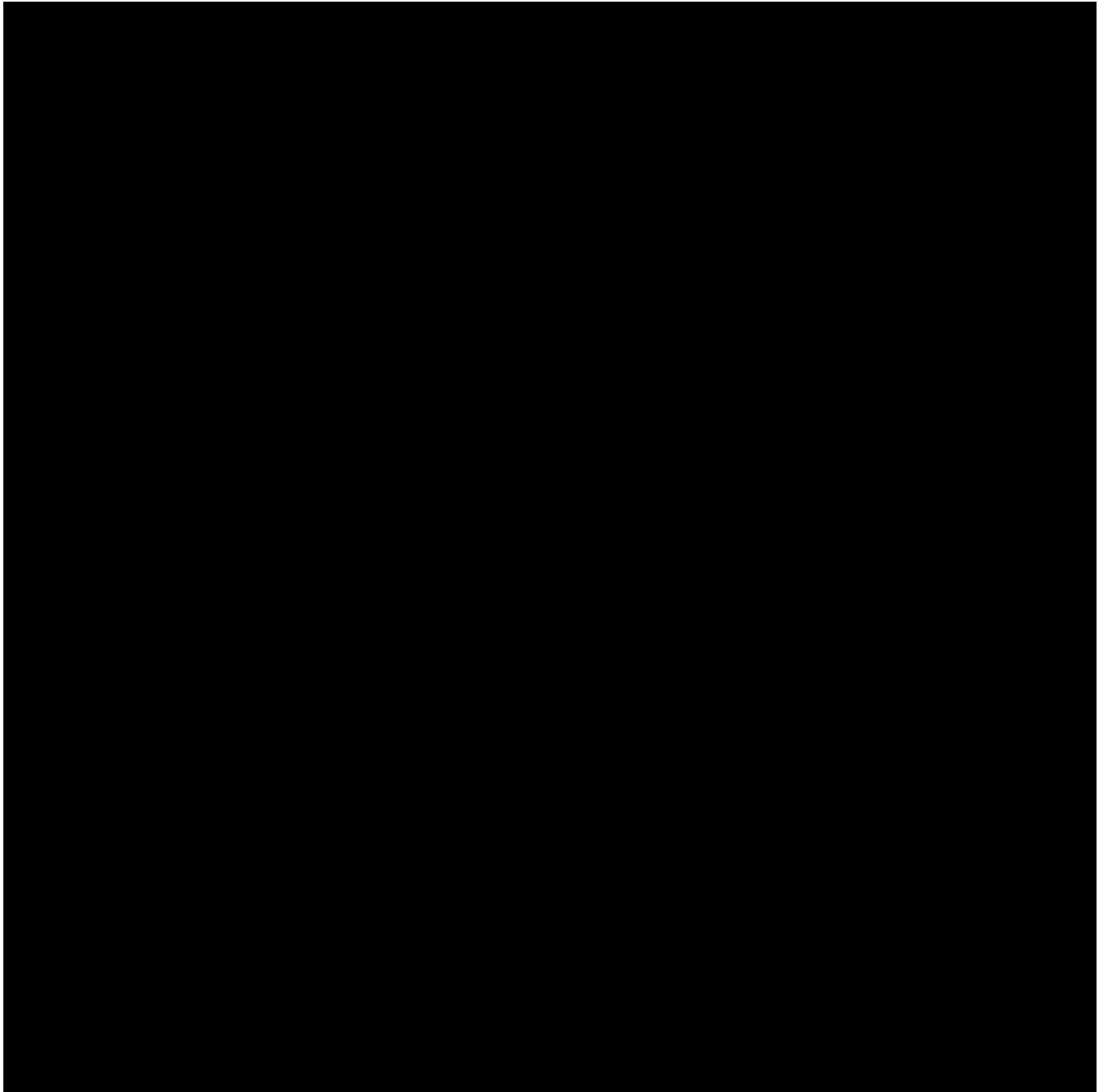


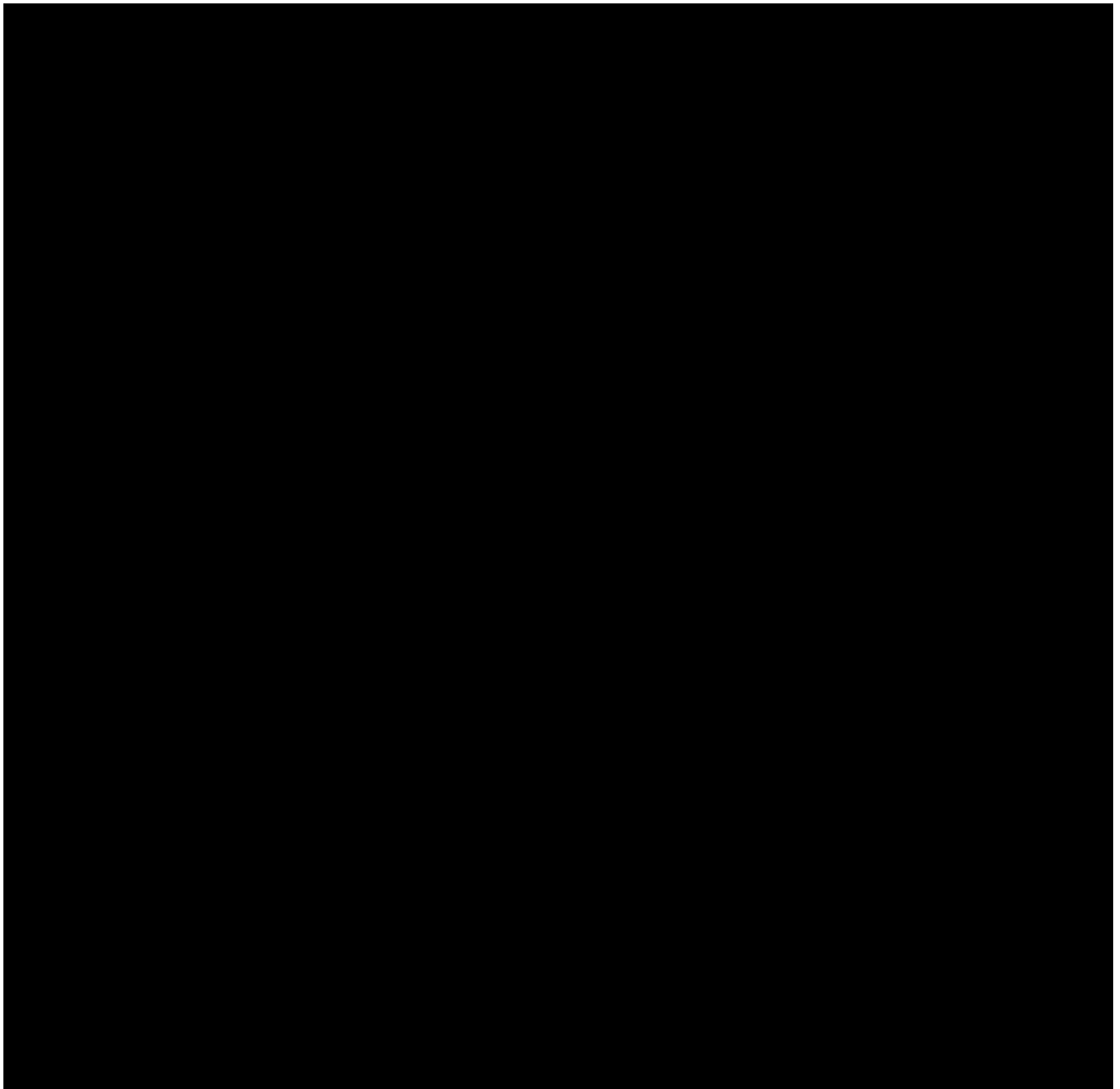


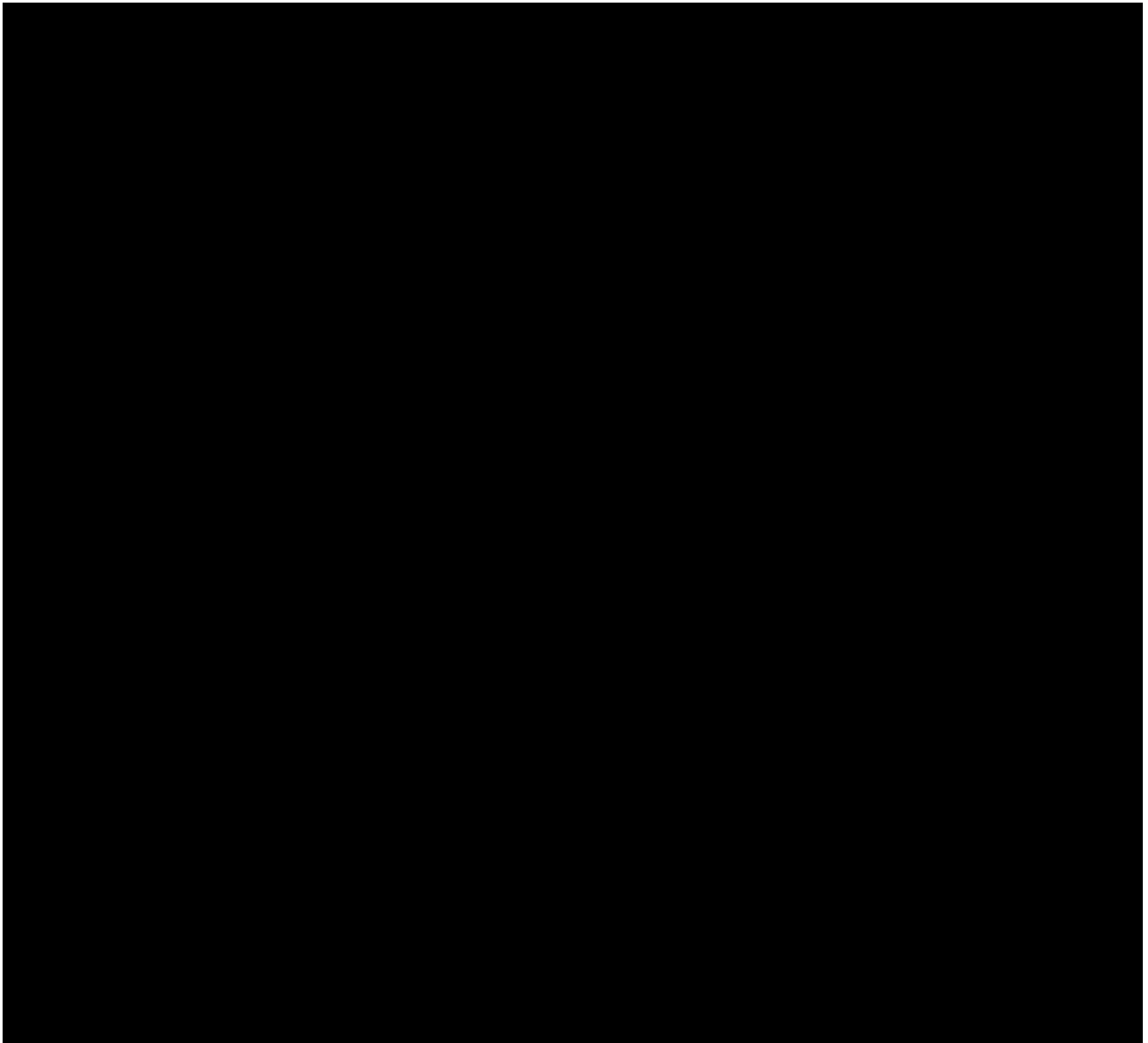




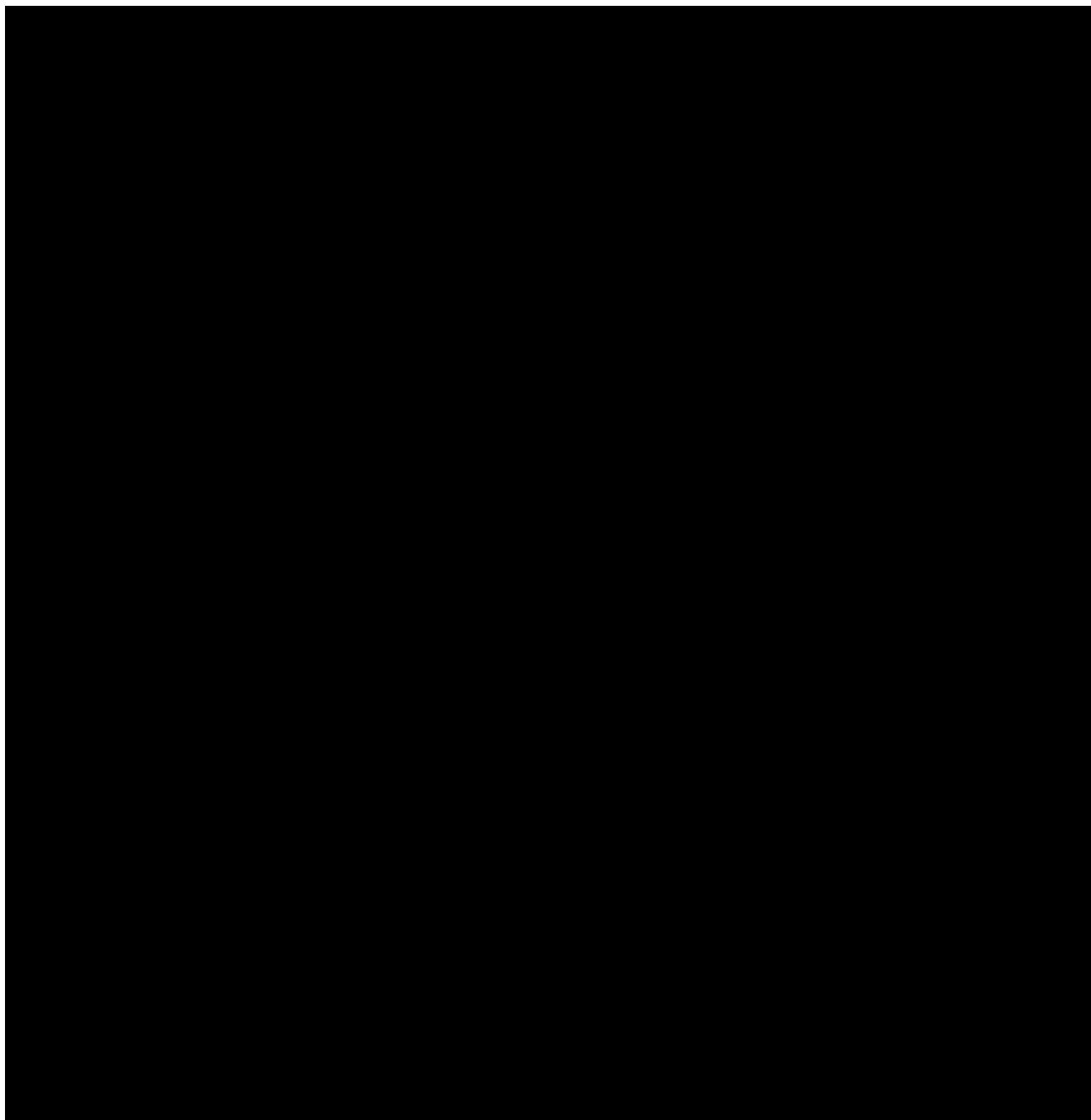


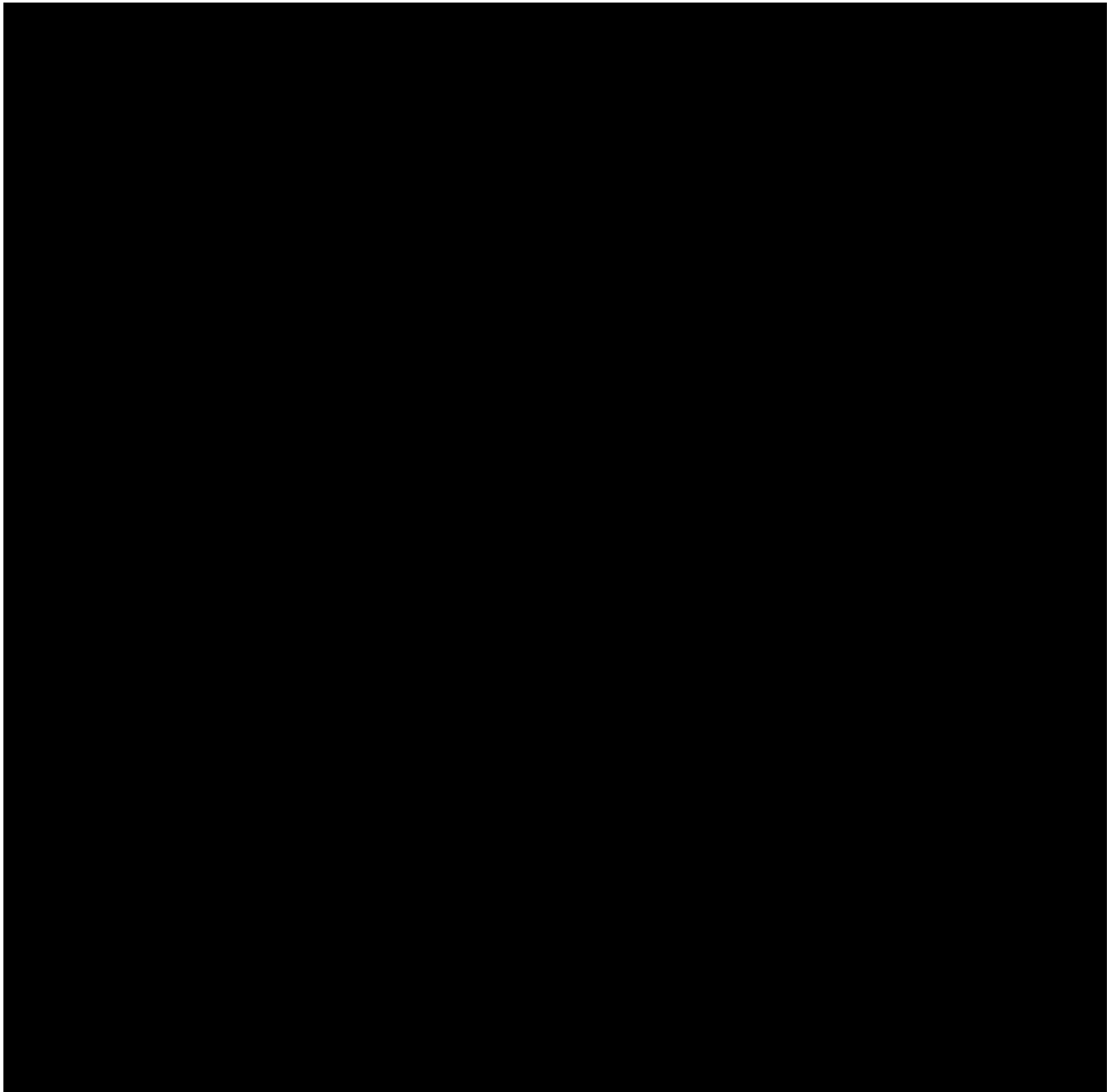


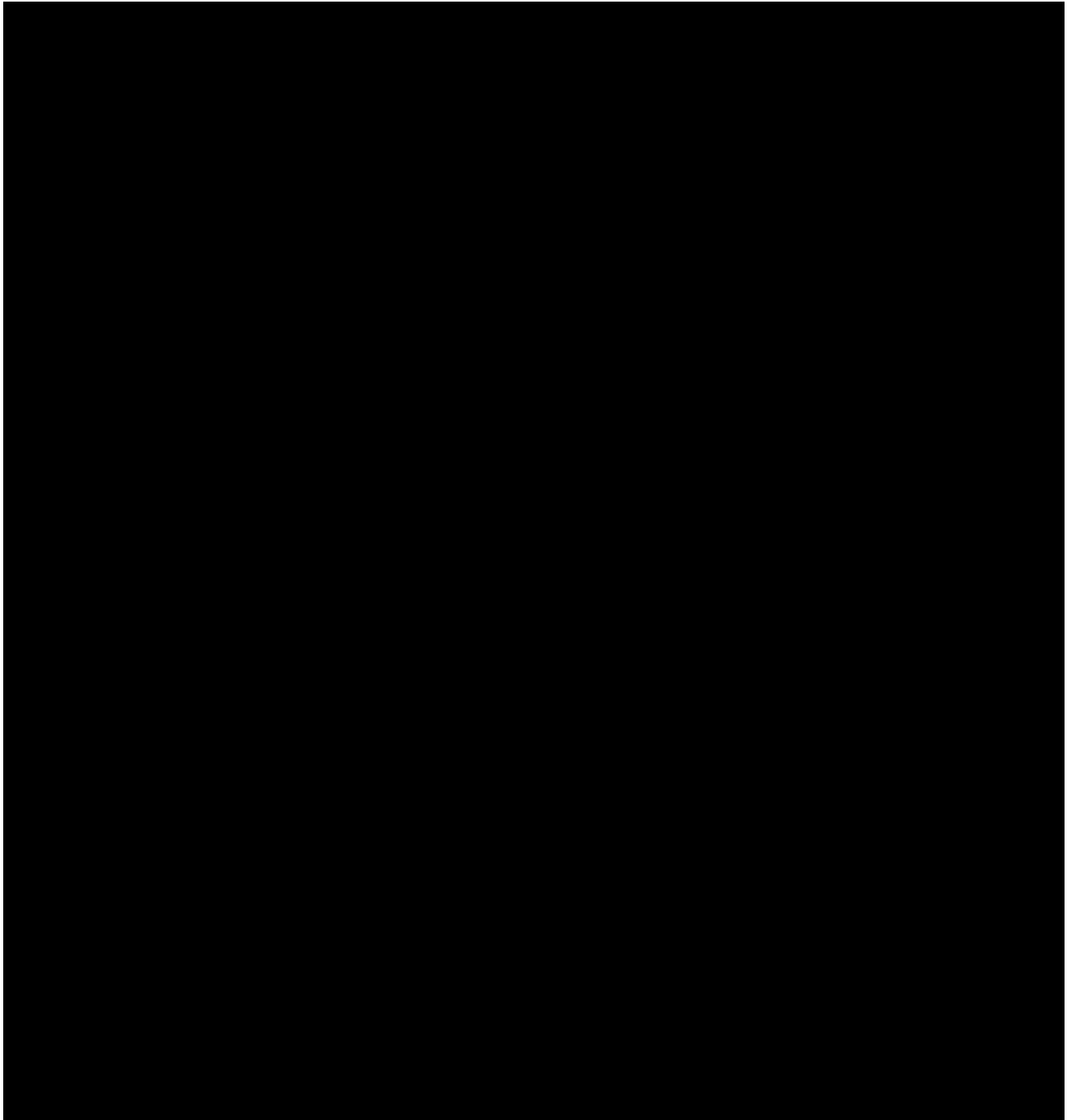


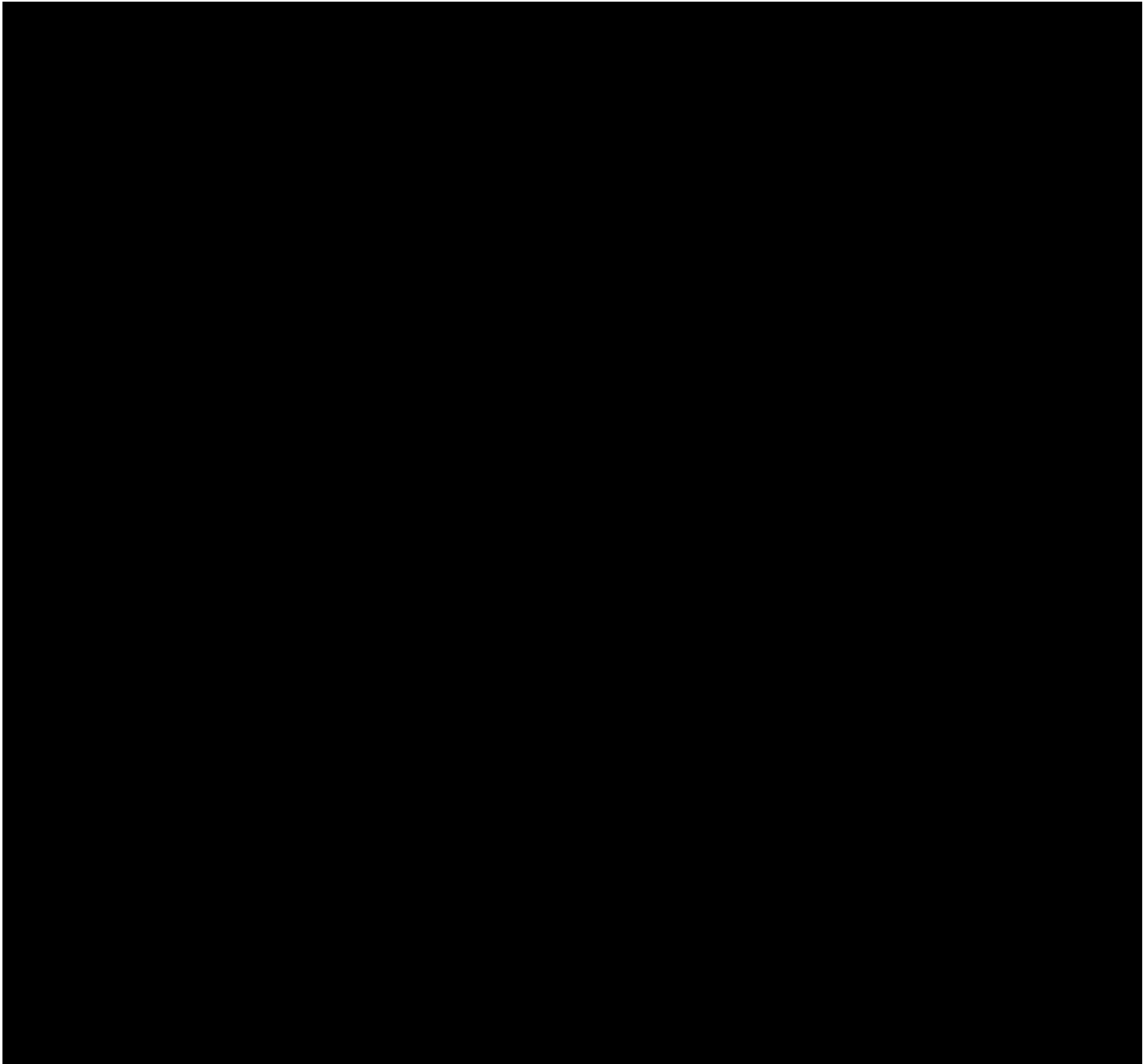












Appendix L STS Query for Patients with STS Mortality Risk Score $\geq 12\%$

Date run: 05DEC2012

Distribution of Baseline Characteristics and Outcomes

Patients undergoing primary isolated mitral valve repair and have STS predicted mortality risk scores $\geq 12\%$
Data collected under v2.61 and v2.73 (2008-2012)

Table: Patient Descriptive Statistics

Variable	Level	Overall (N=463)	
<u>Demographics</u>			
Data version		344	74.30
	2.61		
	2.73	119	25.70
Age	Median	463	75.00
	25th		63.00
	75th		82.00
	Mean		72.10
	STD		12.80
	Min		21.00
	Max		96.00
	Missing(%)		0.00
Age	<75	230	49.68
	>=75	233	50.32
Gender	Male	247	53.35
	Female	216	46.65
Surgery year		88	19.01
	2008		
		92	19.87
	2009		
		101	21.81
	2010		
		134	28.94
	2011		
		48	10.37
	2012		
<u>Risk Factors</u>			
Body Mass Index	Median	459	25.24
	25th		22.04
	75th		29.41
	Mean		26.53
	STD		6.87
	Min		12.61
	Max		75.52
	Missing(%)		0.86
Diabetes	No	240	51.84
	Yes	223	48.16

Variable	Level	Overall (N=463)	
Last Serum Creatinine Pre-operative	Median	461	1.80
	25th		1.30
	75th		3.50
	Mean		2.80
	STD		2.45
	Min		0.44
	Max		14.50
	Missing(%)		0.43
Dialysis for Renal Failure	Missing	1	0.22
	No	294	63.50
	Yes	168	36.29
Renal Function	Missing	3	0.65
	Dialysis	168	36.29
	No dialysis, GFR <15	14	3.02
	No dialysis, GFR 15-29	44	9.50
	No dialysis, GFR 30-59	164	35.42
	No dialysis, GFR 60-89	55	11.88
	No dialysis, GFR 90+	15	3.24
Chronic Lung Disease Reported	Missing	2	0.43
	No	215	46.44
	Yes	246	53.13
Chronic Lung Disease	Missing	2	0.43
	No	215	46.44
	Mild	74	15.98
	Moderate	67	14.47
	Severe	105	22.68
Peripheral Vascular Disease	No	330	71.27
	Yes	133	28.73
Cerebrovascular Disease	No	362	78.19
	Yes	101	21.81
<u>Previous CV Interventions</u>			
Previous Cardiovascular Operations	Missing	2	0.43
	No	279	60.26
	Yes	182	39.31
<u>Pre Operative Cardiac Status</u>			
Myocardial Infarction	No	311	67.17
	Yes	152	32.83
MI / Timing	No Prior MI	311	67.17
	MI / >21 days	114	24.62
	MI / 8-21 days	15	3.24
	MI / 1-7 days	16	3.46
	MI / 6-24 hrs	3	0.65
	MI / <= 6 hrs	4	0.86

Variable	Level	Overall (N=463)	
Congestive Heart Failure	No	59	12.74
	Yes	404	87.26
NYHA Classification(if CHF)	Missing	2	0.50
	I	4	0.99
	II	21	5.20
	III	109	26.98
	IV	268	66.34
NYHA Classification	Missing	61	13.17
	I	4	0.86
	II	21	4.54
	III	109	23.54
	IV	268	57.88
Arrhythmia	No (v2.61) or No/Remote (v2.73)	243	52.48
	Yes (v2.61) or Recent (v2.73)	220	47.52
Atrial fibrillation within 2 weeks (v2.61) or 30 days (2.73)	No	264	57.02
	Yes	199	42.98
Atrial fibrillation within 2 weeks (v2.61)	No	198	57.56
	Yes	146	42.44
Atrial fibrillation within 30 days (v2.73)	No	66	55.46
	Yes	53	44.54
<u>Hemodynamics and Cath</u>			
Ejection Fraction	Median	446	50.50
	25th		35.00
	75th		60.00
	Mean		49.12
	STD		16.04
	Min		10.00
	Max		90.00
	Missing(%)		3.67
<u>Post Operative</u>			
Total Ventilation > 40 Hrs	Missing	22	4.75
	No	284	61.34
	Yes	157	33.91
Initial Ventilation > 40 Hrs	Missing	23	4.97
	No	311	67.17
	Yes	129	27.86
Blood Products Used Postoperatively	Missing	2	0.43
	No	128	27.65
	Yes	333	71.92
Red Blood Cell Units (if Blood Products Used)	Missing	5	1.50
	< 2	78	23.42
	2+	250	75.08

Variable	Level	Overall (N=463)	
<u>In-hosp Complications</u>			
Reop for Valve Dysfunction	No	458	98.92
	Yes	5	1.08
Reop for Bleeding/Temponade	No	438	94.60
	Yes	25	5.40
Reop for Graft Occlusion	No	463	100.00
Reop for Other Cardiac Problem	No	451	97.41
	Yes	12	2.59
Reop for Other Non Cardiac Problem	No	414	89.42
	Yes	49	10.58
Reoperation for Any Reason	Missing	134	28.94
	No	252	54.43
	Yes	77	16.63
Stroke > 24 Hrs	Missing	1	0.22
	No	442	95.46
	Yes	20	4.32
Prolonged Ventilation [A]	Missing	1	0.22
	No	236	50.97
	Yes	226	48.81
Renal Failure [B]	No	421	90.93
	Yes	42	9.07
Perioperative Myocardial Infarction in v2.61 [C]	No	342	99.42
	Yes	2	0.58
<u>Outcomes</u>			
Post-Proc Length of Stay	Median	463	10.00
	25th		7.00
	75th		16.00
	Mean		14.94
	STD		18.99
	Min		0.00
	Max		258.00
	Missing(%)		0.00
Post-Op LOS > 14 days	No	326	70.41
	Yes	137	29.59
In-hospital Mortality	No	400	86.39
	Yes	63	13.61
Operative mortality	No	394	85.10
	Yes	69	14.90
Predicted Risk of Mortality	Median	463	0.17
	25th		0.14
	75th		0.24

Variable	Level	Overall (N=463)
	Mean	0.22
	STD	0.13
	Min	0.12
	Max	0.91
	Missing(%)	0.00

[A] Prolonged ventilation indicates that the patient had prolonged pulmonary total ventilator > 24 hours.

[B] Definition differs for 2.61 and 2.73. See STS data specifications for details.

[C] Perioperative Myocardial Infarction was not collected in v2.73.

Source: /outcomes/sts/sk288/minor/Sethuraman/univtable1.sas

Data Source: cln0712h3.sas7bdat

Date run: 05DEC2012

Distribution of Baseline Characteristics and Outcomes

Patients undergoing primary isolated mitral valve replacement and have STS predicted mortality risk scores $\geq 12\%$
Data collected under v2.61 and v2.73 (2008-2012)

Table: Patient Descriptive Statistics

Variable	Level	Overall (N=2750)	
<u>Demographics</u>			
Data version		2110	76.73
	2.61	640	23.27
	2.73		
Age	Median	2750	73.00
	25th		61.00
	75th		81.00
	Mean		69.88
	STD		13.88
	Min		19.00
	Max		108.00
	Missing(%)		0.00
Age	<75	1505	54.73
	>=75	1245	45.27
Gender	Male	1097	39.89
	Female	1653	60.11
Surgery year		555	20.18
	2008	615	22.36
	2009	619	22.51
	2010	643	23.38
	2011	318	11.56
	2012		
<u>Risk Factors</u>			
Body Mass Index	Median	2745	26.45
	25th		22.64
	75th		31.46
	Mean		27.94
	STD		7.60
	Min		12.45
	Max		83.08
	Missing(%)		0.18
Diabetes	No	1474	53.60
	Yes	1276	46.40
Last Serum Creatinine Pre-operative	Median	2748	1.70
	25th		1.20

Variable	Level	Overall (N=2750)	
	75th		3.20
	Mean		2.59
	STD		2.22
	Min		0.20
	Max		19.10
	Missing(%)		0.07
Dialysis for Renal Failure	Missing	1	0.04
	No	1926	70.04
	Yes	823	29.93
Renal Function	Missing	22	0.80
	Dialysis	823	29.93
	No dialysis, GFR <15	86	3.13
	No dialysis, GFR 15-29	306	11.13
	No dialysis, GFR 30-59	1027	37.35
	No dialysis, GFR 60-89	395	14.36
	No dialysis, GFR 90+	91	3.31
Chronic Lung Disease Reported	Missing	6	0.22
	No	1663	60.47
	Yes	1081	39.31
Chronic Lung Disease	Missing	6	0.22
	No	1663	60.47
	Mild	377	13.71
	Moderate	347	12.62
	Severe	357	12.98
Peripheral Vascular Disease	Missing	2	0.07
	No	2148	78.11
	Yes	600	21.82
Cerebrovascular Disease	Missing	1	0.04
	No	1963	71.38
	Yes	786	28.58
<u>Previous CV Interventions</u>			
Previous Cardiovascular Operations	Missing	9	0.33
	No	1387	50.44
	Yes	1354	49.24
<u>Pre Operative Cardiac Status</u>			
Myocardial Infarction	Missing	2	0.07
	No	1991	72.40
	Yes	757	27.53
MI / Timing	Missing	2	0.07
	No Prior MI	1991	72.40
	MI / Missing Timing	5	0.18
	MI / >21 days	461	16.76
	MI / 8-21 days	88	3.20
	MI / 1-7 days	144	5.24

Variable	Level	Overall (N=2750)	
	MI / 6-24 hrs	34	1.24
	MI / ≤ 6 hrs	25	0.91
Congestive Heart Failure	No	360	13.09
	Yes	2390	86.91
NYHA Classification(if CHF)	Missing	49	2.05
	I	32	1.34
	II	175	7.32
	III	669	27.99
	IV	1465	61.30
NYHA Classification	Missing	409	14.87
	I	32	1.16
	II	175	6.36
	III	669	24.33
	IV	1465	53.27
Arrhythmia	Missing	6	0.22
	No (v2.61) or No/Remote (v2.73)	1395	50.73
	Yes (v2.61) or Recent (v2.73)	1349	49.05
Atrial fibrillation within 2 weeks (v2.61) or 30 days (2.73)	Missing	7	0.25
	No	1535	55.82
	Yes	1208	43.93
Atrial fibrillation within 2 weeks (v2.61)	Missing	2	0.09
	No	1164	55.17
	Yes	944	44.74
Atrial fibrillation within 30 days (v2.73)	Missing	5	0.78
	No	371	57.97
	Yes	264	41.25
<u>Hemodynamics and Cath</u>			
Ejection Fraction	Median	2611	55.00
	25th		45.00
	75th		62.00
	Mean		53.21
	STD		13.74
	Min		5.00
	Max		90.00
	Missing(%)		5.05
<u>Post Operative</u>			
Total Ventilation > 40 Hrs	Missing	109	3.96
	No	1612	58.62
	Yes	1029	37.42
Initial Ventilation > 40 Hrs	Missing	122	4.44
	No	1772	64.44
	Yes	856	31.13
Blood Products Used Postoperatively	Missing	11	0.40

Variable	Level	Overall (N=2750)	
	No	545	19.82
	Yes	2194	79.78
Red Blood Cell Units (if Blood Products Used)	Missing	26	1.19
	< 2	439	20.01
	2+	1729	78.81
<u>In-hosp Complications</u>			
Reop for Valve Dysfunction	Missing	10	0.36
	No	2731	99.31
	Yes	9	0.33
Reop for Bleeding/Temponade	Missing	7	0.25
	No	2554	92.87
	Yes	189	6.87
Reop for Graft Occlusion	Missing	8	0.29
	No	2742	99.71
Reop for Other Cardiac Problem	Missing	9	0.33
	No	2645	96.18
	Yes	96	3.49
Reop for Other Non Cardiac Problem	Missing	9	0.33
	No	2393	87.02
	Yes	348	12.65
Reoperation for Any Reason	Missing	698	25.38
	No	1477	53.71
	Yes	575	20.91
Stroke > 24 Hrs	Missing	9	0.33
	No	2615	95.09
	Yes	126	4.58
Prolonged Ventilation [A]	Missing	8	0.29
	No	1291	46.95
	Yes	1451	52.76
Renal Failure [B]	Missing	8	0.29
	No	2338	85.02
	Yes	404	14.69
Perioperative Myocardial Infarction in v2.61 [C]	Missing	8	0.38
	No	2072	98.20
	Yes	30	1.42
<u>Outcomes</u>			
Post-Proc Length of Stay	Median	2748	12.00
	25th		8.00
	75th		20.00
	Mean		16.16
	STD		14.62
	Min		0.00
	Max		149.00
	Missing(%)		0.07

Variable	Level	Overall (N=2750)	
Post-Op LOS > 14 days	No	1671	60.76
	Yes	1079	39.24
In-hospital Mortality	Missing	3	0.11
	No	2282	82.98
	Yes	465	16.91
Operative mortality	No	2257	82.07
	Yes	493	17.93
Predicted Risk of Mortality	Median	2750	0.18
	25th		0.14
	75th		0.26
	Mean		0.22
	STD		0.12
	Min		0.12
	Max		0.86
	Missing(%)		0.00

[A] Prolonged ventilation indicates that the patient had prolonged pulmonary total ventilator > 24 hours.

[B] Definition differs for 2.61 and 2.73. See STS data specifications for details.

[C] Perioperative Myocardial Infarction was not collected in v2.73.

Source: /outcomes/sts/sk288/minor/Sethuraman/univtable5.sas

Data Source: cln0712h3.sas7bdat